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Cascade assembling of pyrazolin-5-ones and benzylidenemalononitriles: the facile and efficient approach to medicinally relevant spirocyclopropylpyrazolone scaffold

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Abstract: A new cascade reaction provides a direct transformation of pyrazolin-5-ones and benzylidenemalononitriles by the action of bromine into substituted spirocyclopropylpyrazolones in 60–88% yields. This process can be realized in two variants, namely, (1) by treatment with bromine in the presence of base and (2) by treatment with bromine only with heating. These facile and efficient one-step cascade processes lead to the spirocyclopropylpyrazolone framework, which is present in a perspective class of compounds with prominent pharmacological and physiological activity.

Keywords: activated olefins; cascade reaction; cyclization; pyrazoline-5-one; spirocyclopropylpyrazolone.

Introduction

The cyclopropyl group is an important structural unit in many synthetic and naturally occurring compounds which are characterized by a wide spectrum of biologic properties ranging from enzyme inhibition to herbicidal, antibiotic, antitumor and antiviral activities [1–4]. The spirocyclopropyl moiety jointed with a heterocyclic fragment has also aroused a special interest because of the wide range of pharmacological applications of such compounds. In particular, fused spirocyclopropyl heterocycles have been recognized as α-L-fucosidase [5], and HIV-1 non-nucleoside reverse transcriptase inhibitors [6]. Among them, bis(spiro-2,4-dihydro-3*H*-pyrazol-3-one)cyclopropanes (2,3,8,9-tetraazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione ring system) are effective agents against *P. oryzae* and *H. oryzae* fungi that are responsible for rice crop diseases [7]. Recently, the corresponding 4,10-dimethyl-2,8,11-triphenyl-2,3,8,9-tetraazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione was patented as advanced glycation end products (AGE) formation inhibitor intended for treatment of human schizophrenia [8]. Thus, spirocyclopropylpyrazolones appear to be of interest because they incorporate the spiro scaffold containing cyclopropane and 2-pyrazolin-5-one groups [9]. These moieties are promising with the respect to biological responses.

The discovery of novel and efficient synthetic methodologies is one of the main points of research activity in the field of modern organic, medicinal and combinatorial chemistry [10–12]. One of the main approaches in this area involves combination of two or more distinct reactions into a single transformation, producing cascade reactions as a sequential reaction process [13, 14]. Thereby, cascade reactions have significant economical and ecological benefits [15, 16], especially for the design and construction of elaborate heterocyclic frameworks possessing enhanced ‘drug-like’ properties [17–19]. Considering our experience in cascade synthesis of cyclopropane rings [20–22], as well as certain biomedical applications of cyclopropylheterocycles mentioned above, we were prompted to design a convenient methodology for ‘one-pot’ transformation of pyrazolin-5-ones and activated olefins into a spirocyclopropylpyrazolone scaffold.

Results and discussion

We wish to report our results on the novel efficient cascade assembling of pyrazoline-5ones **1a**,**b** and activated olefins **2a-k** into substituted spirocyclopropylpyrazolones **3a-o** (Scheme 1, Tables 1 and 2). First, the ‘one-pot’ cascade

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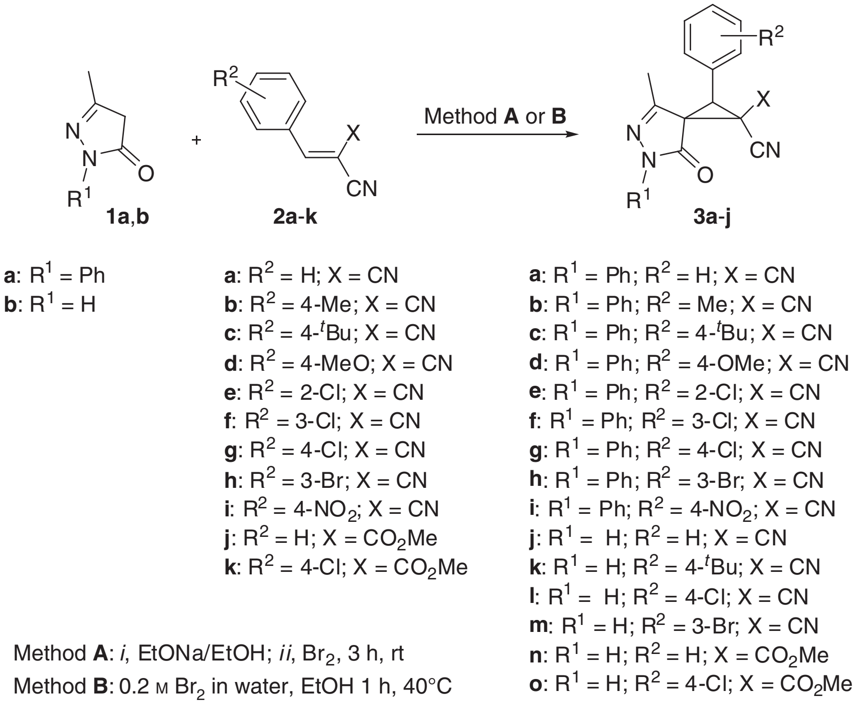


Scheme 1

Table 1 Cascade transformation of pyrazoline-5-one **1a** and benzylidenemalononitrile **2a** into substituted spirocyclopropylpyrazolone **3a**.[a]

Entry	Quantity of EtONa (equivalents)	Yield of 3a[b] (%)
1	1.0	52
2	1.2	68
3	1.4	76
4	1.6	69
5	2.0	63

[a] 10 mmol of **1a**, 10 mmol of **2a**, 10 mmol of bromine, 30 mL of ethanol, time of the reaction: 3 h.

[b] Isolated yield.

transformation of pyrazoline-5-one **1a** and benzylidenemalononitrile **2a** into spirocyclopropylpyrazolone **3a** was studied by the action of bromine in ethanol in the presence of EtONa as base (Method **A**, Table 1). The best yield of spirocyclopropylpyrazolone **3a** (76%) was obtained when 1.4 equivalents of EtONa were used (Entry 3, Table 1). The increase of the amount of EtONa (Entries 4 and 5, Table 1) resulted in a decrease of the cyclization yield. Under the optimal conditions, pyrazoline-5-ones **1a**,**b** and activated olefins **2a-k** were transformed into spirocyclopropylpyrazolones **3a-o** in 63–88% yields (Method **A**, Table 2).

Recently, we have found that the base can be excluded from this cascade synthesis [22]. Thus, we carried out transformation of pyrazoline-5-ones **1a**,**b** and activated olefins **2a-k** into substituted spirocyclopropylpyrazolones **3a-o** by the use of bromine only (Method **B**, Scheme 2; Table 2). The yields of spirocyclopropylpyrazolones **3a-o** under conditions of the method **B** are generally slightly lower, in the range of 60–80%.

The structures of **3c-e** and two diastereoisomers of **3a**,**b**,**f-i** were established by NOESY experiments (Figure 1). The NOESY spectrum of the major (2*R**,3*S**) isomer shows interactions between the CH_3 group and *ortho*-H atoms of both phenyl rings, as well as interactions between a proton in the cyclopropane ring and *ortho*-H atoms of both phenyl rings. In the minor (2*R**,3*R**) isomer of **3a**,**b**,**f-i** the interactions are observed for the CH_3 group and the H proton of the cyclopropane ring as well as between the latter and *ortho*-H atoms of the phenyl substituent. The NOESY results are fully consistent with the (2*R**,3*S**) configuration for **3j**,**k** and the major isomer of **3l**,**m** (Figure 2). The (1*S**,2*R**,3*R**)-structures for **3n**,**o** were established earlier on the data of the X-ray diffraction study [23].

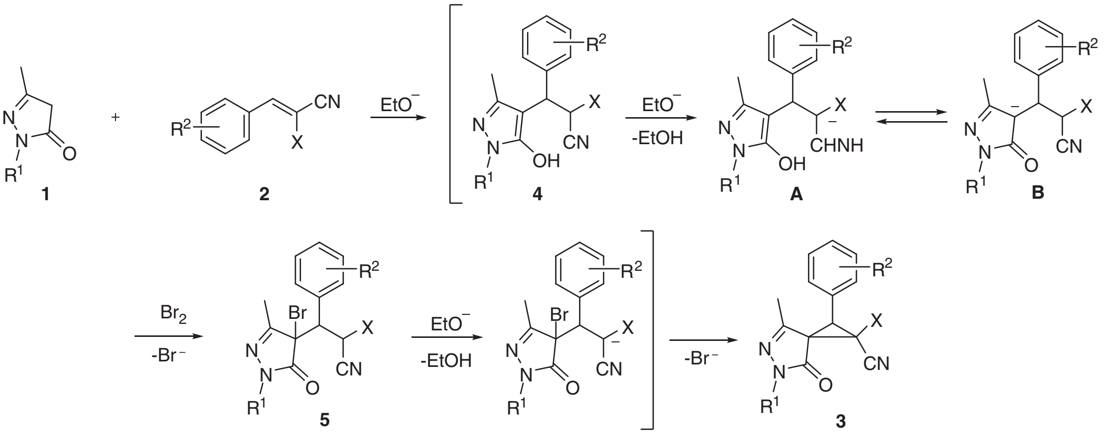
With the results above taken into consideration and the available literature data on mechanisms of the transformation of carbonyl compounds and activated olefins into cyclic structures [20–22], the following mechanism for the cascade addition of pyrazolin-5-ones **1** to activated olefins **2** with further cyclization into substituted spirocyclopropylpyrazolones **3** in the presence of EtONa is proposed (Method **A**, Scheme 2).

Table 2 Cascade transformation of pyrazoline-5-ones **1a,b** and activated olefins **2a-k** into substituted spirocyclopropylpyrazolone **3a-o.**[a]

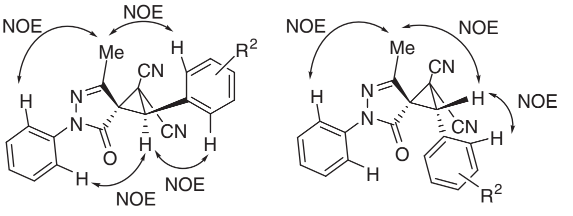
Entry	Pyrazoline-5-one	R¹	Activated olefin	R²	X	Spirocyclopropylpyrazolone, method, yield, ratio of isomers[b]
1		Ph	**2a**	H	CN	**3a**, **A** 76 (4:1); **B** 70 (4:1)
2		Ph	**2b**	4-Me	CN	**3b**, **A** 86 (3:1); **B** 75 (3:1)
3		Ph	**2c**	4-*t*Bu	CN	**3c**, **A** 70, **B** 65
4		Ph	**2d**	4-MeO	CN	**3d**, **A** 72; **B** 63
5		Ph	**2e**	2-Cl	CN	**3e**, **A** 77; **B** 72
6		Ph	**2f**	3-Cl	CN	**3f**, **A** 82 (5:2); **B** 75 (3:1)
7		Ph	**2g**	4-Cl	CN	**3g**, **A** 88 (3:1); **B** 81 (4:1)
8		Ph	**2h**	3-Br	CN	**3h**, **A** 78 (3:1); **B** 63 (4:1)
9		Ph	**2i**	4-NO_2	CN	**3i**, **A** 71 (4:3); **B** 65 (2:1)
10		H	**2a**	H	CN	**3j**, **A** 75; **B** 71
11		H	**2c**	4-*t*Bu	CN	**3k**, **A** 66, **B** 61
12		H	**2g**	4-Cl	CN	**3l**, **A** 73 (4:1); **3l**, **B** 66 (4:1)
13		H	**2h**	3-Br	CN	**3m**, **A** 81 (3:1); **B** 75 (4:1)
14		H	**2j**	H	CO_2Me	**3n**, **A** 63; **B** 60
15		H	**2k**	4-Cl	CO_2Me	**3o**, **A** 65, **B** 62

[a] Method **A**: 10 mmol of **1**, 10 mmol of **2**, 10 mmol of bromine, 14 mmol of EtONa, 30 mL of EtOH, ambient temperature, 3 h. Method **B**: 10 mmol of **1**, 10 mmol of **2**, 50 mL of 0.2 м bromine in water, 40 mL of EtOH, 40°C, 1 h.

[b] Isolated yields.



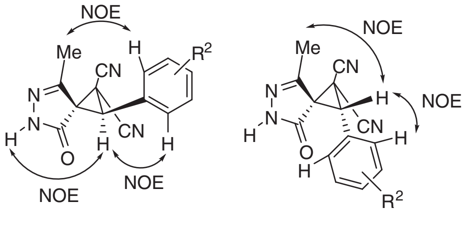
Scheme 2



(2*R**,3*S**)
Major diastereoisomer

(2*R**,3*R**)
Minor diastereoisomer

Figure 1 NOESY interactions for spirocyclopropylpyrazolones **3a-i**.

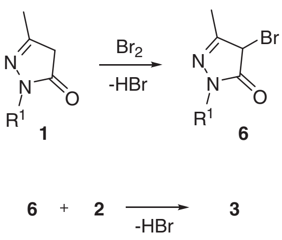


(2*R**,3*S**)
Major diastereoisomer

(2*R**,3*R**)
Minor diastereoisomer

Figure 2 NOESY interactions for **3j-m**.

In the first step, Michael addition of pyrazolin-5-one **1** to activated olefin **2** catalyzed by ethoxide anion leads to the adduct **4** which in the presence of another ethoxide anion is transformed into anion **A**, which exists in equilibrium with anion **B**. Then, bromination leads to brominated arylpropionitrile **5**, which in the presence of ethoxide anion is cyclized into spirocyclopropylpyrazolone **3**. In the mechanism on Scheme 2, two moles of ethoxide



Scheme 3

anion are needed for one mole of pyrazolin-5-one **1**. Actually, under the optimized conditions, only 1.4 equivalents of ethoxide are needed. This quantity is sufficient to ensure 70% yield of spirocyclopropylpyrazolone **3**. At the same time, the best 88% yield was obtained in the case of spirocyclopropylpyrazolone **3g**. Thus, brominated arylpropionitrile **5** is a reasonably strong acid which can be ionized to the corresponding anion for further cyclization. The cyclizations of brominated C-H acids of such type in ethanol without adding ethoxide anion have been reported [24].

In the absence of base (Method **B**), bromination of pyrazolin-5-ones **1** affords bromo-substituted pyrazolin-5-one **6** (Scheme 3), which is a reasonably strong CH-acid and can under heating provide a sufficient concentration of anion of bromo-substituted pyrazolin-5-one **B** in ethanol to ensure further Michael addition and cyclization into spirocyclopropylpyrazolone **3**.

Conclusion

The new cascade reaction of pyrazolin-5-ones and activated olefins in the presence of bromine results in the selective formation of substituted spirocyclopropylpyrazolones in 60–88% yields. This is a perspective class of compounds with prominent pharmacological and physiological activity. The procedure utilizes inexpensive reagents and is easily carried out. Compared to the previously described [24] electrochemical method, this process is much simpler experimentally.

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded with a Bruker AM-300 at ambient temperature in DMSO-d_6 solutions. IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Electron-impact mass spectra were obtained at 70 eV on a Finningan MAT INCOS 50 spectrometer.

Typical procedures for cascade synthesis of products 3

Method A To a 30 mL of ethanolic suspension of pyrazolin-5-one **1** (10 mmol) and activated olefin **2** (10 mmol) in a 50 mL beaker, 14 mmol of sodium ethoxide in 15 mL of ethanol was added during 1 min. Then 10 mmol of bromine was added during 1 min without external cooling. The mixture was magnetically stirred at room temperature for 3 h. Then the precipitate of **3** was filtered off, washed with water and dried in a desiccator over P_2O_5.

Method B To a 40 mL of ethanolic suspension of pyrazolin-5-one **1** (10 mmol) and activated olefin **2** (10 mmol) in a 100 mL three-necked flask, 50 mL of 0.2 M bromine in water (10 mmol) was added during 5 min. The mixture was magnetically stirred at 40°C for 1 h. Then the precipitate of **3** was filtered off, washed with water and dried in a desiccator over P_2O_5.

4-Methyl-7-oxo-2,6-diphenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3a) White solid; yield 2.48 g (76%); diastereomeric ratio 4:1; mp 187–189°C (Lit. [23] mp 188–189°C); ^{1}H NMR: major diastereoisomer: δ_H 1.71 (s, 3H, CH$_3$), 4.20 (s, 1H, CH), 7.38–7.52 (m, 8H, Ar), 7.95 (d, *J* = 7.9 Hz, 2H, Ar); minor diastereoisomer: δ_H 2.35 (s, 3H, CH$_3$), 4.94 (s, 1H, CH), 7.19–7.35 (m, 8H, Ar), 7.85 (d, *J* = 7.9 Hz, 2H, Ar).

4-Methyl-2-(4-methylphenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonit-rile (3b) White solid; yield 2.93 g (86%); diastereomeric ratio 3:1; mp 175–178°C; IR for a mixture: ν_{max} 3314, 2996, 2253, 1718, 1597, 1501, 1373, 1326, 1179, 758 cm^{-1}; MS for a mixture: *m/z* (%) 340 ([M$^+$], 26), 276 (3), 221 (4), 180 (18), 165 (17), 115 (12), 91 (28), 77 (100), 51 (49), 39 (22); ^{1}H NMR: major diastereoisomer: δ_H 1.88 (s, 3H, CH$_3$), 2.41 (s, 3H, CH$_3$), 3.93 (s, 1H, CH), 7.20–7.32 (5H, m, Ar), 7.43–7.51 (2H, m, Ar), 7.94–8.01 (2H, m, Ar); minor diastereoisomer: δ_H 2.36 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 3.99 (s, 1H, CH), 7.20–7.32 (5H, m, Ar), 7.38–7.43 (2H, m, Ar), 7.87–7.94 (2H, m, Ar); ^{13}C NMR: major diastereoisomer: δ_C 16.3, 19.9, 20.7, 42.7, 44.7, 110.8, 111.3, 118.2 (2C), 124.6, 125.3, 129.0 (2C), 129.4 (2C), 129.7 (2C), 137.7, 139.0, 151.9, 165.0; minor diastereoisomer: δ_C 14.0, 20.0, 20.7, 40.7, 44.5, 109.3, 113.0, 118.2 (2C), 124.3, 125.2, 129.0 (2C), 129.5 (2C), 129.7 (2C), 138.1, 139.0, 153.8, 163.1. Anal. for a mixture. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 73.96; H, 4.68; N, 16.51.

(2*R,3*S**)-2-(4- *tert* -Butylphenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3c)** White solid; yield 3.01 g (78%); mp 190–192°C; IR: ν_{max} 2964, 2869, 2251, 1719, 1597, 1502, 1374, 1328, 756 cm^{-1}; MS: *m/z* (%) 382 ([M$^+$], 8), 318 (1), 207 (15), 185 (6), 140 (5), 119 (6), 91 (26), 77 (100), 67 (39), 57 (57); ^{1}H NMR: δ_H 1.29 (c, 9H, CH$_3$), 1.72 (s, 3H, CH$_3$), 4.15 (s, 1H, CH), 7.35–7.55 (m, 5H, Ar), 7.85 (d, *J* = 8.0 Hz, 2H, Ar), 7.95 (d, *J* = 8.0 Hz, 2H, Ar); ^{13}C NMR: δ_C 16.6, 20.2, 31.3 (3C), 34.8, 40.9, 44.8, 111.2, 111.7, 118.6, 120.2, 125.0, 125.9 (2C), 129.3 (2C), 129.8 (2C), 138.1 (2C), 151.5, 152.4, 165.4. Anal. Calcd for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65. Found: C, 75.28; H, 5.68; N, 14.71.

(2*R,3*S**)-2-(4-Methoxyphenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3d)** White solid; 2.57 g (72%); mp 219–221°C; IR: ν_{max} 2984, 2254, 1715, 1595, 1518, 1493, 1326, 1257, 1181, 1025, 762 cm^{-1}; MS: *m/z* (%) 356 ([M$^+$], 57), 292 (11), 251 (9), 196 (61), 181 (28), 153 (39), 119 (11), 91 (25), 77 (100), 67 (25); 1H NMR: δ_H 1.73 (c, 3H, CH$_3$), 3.78 (c, 3H, CH$_3$), 4.07 (c, 1H, CH), 7.03 (d, *J* = 8.1 Hz, 2H, Ar), 7.35–7.55 (m, 5H, Ph), 7.91 (d, *J* = 8.1 Hz, 2H, Ar); ^{13}C NMR: δ_C 16.6, 20.4, 40.8, 44.9, 55.4, 111.2, 111.7, 114.1 (2C), 118.5 (2C), 119.3, 125.5, 129.3 (2C), 131.6 (2C), 138.1, 152.2, 159.7, 165.4. Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.59; H, 4.58; N, 15.61.

(2*R,3*S**)-2-(2-Chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3e)** White solid; yield 2.78 g (77%); mp: 155–157°C; IR: ν_{max} 3411, 2973, 2249, 1714, 1595, 1493, 1329, 1119, 753, 692 cm^{-1}; MS: *m/z* (%) 362 ([M$^+$], 6), 360 ([M$^+$], 19), 325 (12), 261 (4), 206 (5), 165 (21), 119 (14), 91 (19), 77 (100), 67 (41); ^{1}H NMR: δ_H 1.85 (s, 3H, CH_3), 3.77 (s, 1H, CH), 7.27–7.32 (m, 1H, Ar), 7.42–7.57 (m, 5H, Ar), 7.61–7.68 (m, 1H, Ar), 7.99 (m, 2H, Ar); ^{13}C NMR: δ_C 15.9, 20.4, 41.2, 44.7, 110.6, 111.2, 118.3 (2C), 125.5, 126.0, 127.6, 129.1 (2C), 129.8, 131.5, 131.6, 134.4, 137.5, 151.9, 164.8. Anal. Calcd for $C_{20}H_{13}ClN_4O$: C, 66.58; H, 3.63; Cl, 9.83; N, 15.53. Found: C, 66.63; H, 3.49; Cl, 9.67; N, 15.45.

2-(3-Chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbo-nitrile (3f) White solid; yield 2.96 g (82%); diastereomeric ratio 5:2; mp 164–167°C; IR: ν_{max} 3435, 2995, 2249, 1727, 1596, 1500, 1331, 1118, 758, 578 cm^{-1}; MS: *m/z* (%) 362 ([M$^+$], 8), 360 ([M$^+$], 27), 296 (2), 206 (5), 185 (26), 165 (30), 119 (22), 91 (20), 77 (100), 67 (32); ^{1}H NMR: major diastereoisomer: δ_H 1.93 (s, 3H, CH_3), 3.94 (s, 1H, CH), 7.53–7.29 (m, 7H, Ar), 7.95–8.03 (m, 2H, Ar); minor diastereoisomer: δ_H 2.40 (s, 3H, CH_3), 3.98 (s, 1H, CH), 7.53–7.29 (m, 7H, Ar), 7.88–7.94 (m, 2H, Ar); ^{13}C NMR: major diastereoisomer: δ_C 16.3, 20.0, 41.6, 44.6, 110.6, 111.2, 118.2 (2C), 125.3, 128.7, 129.0 (2C), 129.4, 129.8, 130.0, 130.6, 133.4, 137.7, 151.3, 164.9; minor diastereoisomer: δ_C 14.0, 20.9, 41.6, 44.4, 109.2, 112.8, 118.3 (2C), 125.3, 128.6, 129.0 (2C), 129.7, 129.8, 130.2, 130.6, 132.8, 137.7, 153.7, 163.1. Anal. for a mixture: Calcd for $C_{20}H_{13}ClN_4O$: C, 66.58; H, 3.63; Cl, 9.83; N, 15.53. Found: C, 66.45; H, 3.55; Cl, 9.73; N, 15.39.

2-(4-Chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbo-nitrile (3g) White solid; yield 3.18 g (88%); diastereomeric ratio 3:1; mp 169–172°C; IR: ν_{max} 3436, 2964, 2252, 1725, 1596, 1495, 1328, 1089, 761, 693 cm^{-1}; MS: *m/z* (%) 362 ([M$^+$], 1), 360 ([M$^+$], 4), 296 (1), 200 (3), 185 (8), 165 (17), 119 (13), 91 (19), 77 (100), 67 (38); ^{1}H NMR: major diastereoisomer: δ_H 1.89 (s, 3H, CH_3), 3.91 (s, 1H, CH), 7.27–7.32 (m, 1H, Ar), 7.35 (d, *J* = 8.2 Hz, 2H, Ar), 7.42–7.54 (m, 4H, Ar), 7.96 (d, *J* = 8.2 Hz, 2H, Ar); minor diastereoisomer: δ_H 2.39 (s, 3H, CH_3), 3.96 (s, 1H, CH), 7.27–7.32 (m, 1H, Ar), 7.40 (d, *J* = 8.2 Hz, 2H, Ar), 7.42–7.54 (m, 4H, Ar), 7.88 (d, *J* = 8.2 Hz, 2H, Ar); ^{13}C NMR: major diastereoisomer: δ_C 16.4, 20.0, 41.9, 44.7, 110.7, 111.2, 118.2 (2C), 125.3, 126.7, 128.4, 128.9 (3C), 131.9 (2C), 134.3, 137.7, 151.4, 164.9; minor diastereoisomer: δ_C 14.1, 20.9, 41.9, 44.5, 109.2, 112.8, 118.2 (2C), 125.3, 126.4, 128.4, 129.0 (3C), 131.7 (2C), 133.6, 137.7, 153.7, 163.0. Anal. for a mixture: Calcd for $C_{20}H_{13}ClN_4O$: C, 66.58; H, 3.63; Cl, 9.83; N, 15.53. Found: C, 66.49; H, 3.51; Cl, 9.68; N, 15.35.

2-(3-Bromophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbo-nitrile (3h) White solid; yield 3.16 g (78%); diastereomeric ratio 3:1; mp 198–200°C; IR: ν_{max} 3059, 3015, 2249, 1726, 1595, 1499, 1372, 1330, 1325, 757 cm^{-1}; MS: *m/z* (%) 406 ([M$^+$], 99), 404 ([M$^+$], 100), 342 (50), 340 (61), 186 (21), 185 (34), 165 (23), 153 (29), 119 (24), 91 (61), 77 (81); ^{1}H NMR: major diastereoisomer: δ_H 1.74 (c, 3H, CH_3), 4.18 (c, 1H, CH), 7.39–7.62 (m, 5H, Ar), 7.83–7.93 (m, 3H, Ar), 8.03 (c, 1H, Ar); minor diastereoisomer: δ_H 2.33 (c, 3H, CH_3), 4.94 (c, 1H, CH), 7.20–7.42 (m, 6H, Ar), 7.68 (d, *J* = 7.5 Hz, 2H, Ar), 7.96 (c, 1H, Ar); ^{13}C NMR: major diastereisomer: δ_C 16.6, 20.3, 41.8, 44.8, 110.9, 111.6, 118.5 (2C), 122.1, 125.6, 129.2 (2C), 129.4, 130.7, 131.9, 132.6, 133.1, 151.5, 163.4, 165.2; minor diastereoisomer: δ_C 14.4, 21.2, 41.9, 44.9, 109.5, 113.1, 118.4 (2C), 121.6, 125.3, 129.3 (2C), 129.5, 131.2, 132.2, 132.8, 134.3, 154.0, 163.9, 165.9. Anal. for a mixture. Calcd for $C_{20}H_{13}BrN_4O$: C, 59.28; H, 3.23; Br, 19.72; N, 13.83. Found: C, 59.09; H, 3.29; Br, 19.57; N, 13.95.

4-Methyl-2-(4-nitrophenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3i) White solid; yield 2.64 g (71%); diastereomeric ratio 4:3; mp 161–163°C; IR: ν_{max} 3434, 3116, 2232, 1722, 1501, 1349, 1118, 1006, 760, 693 cm^{-1}; MS: *m/z* (%) 371 ([M$^+$], 26), 324 (6), 254(2), 199 (16), 153 (25), 119 (20), 91 (21), 77 (100), 67 (30), 51 (32); ^{1}H NMR: major diastereoisomer: δ_H 1.70 (s, 3H, CH_3), 4.33 (s, 1H, CH), 7.26–7.32 (m, 1H, Ar), 7.49–7.56 (m, 2H, Ar), 7.80 (d, *J* = 8.7 Hz, 2H, Ar), 7.88–7.94 (m, 2H, Ar), 8.33 (d, *J* = 8.7 Hz, 2H, Ar); minor diastereoisomer: δ_H 2.27 (s, 3H, CH_3), 5.10 (s, 1H, CH), 7.21–7.26 (m, 1H, Ar), 7.42–7.49 (m, 2H, Ar), 7.76–7.85 (m, 2H, Ar), 7.80 (d, *J* = 8.7 Hz, 2H, Ar), 8.33 (d, *J* = 8.7 Hz, 2H, Ar); ^{13}C NMR: major diastereisomer: δ_C 16.3, 21.0, 39.7, 44.6, 109.2, 112.8, 118.5 (2C), 123.4 (2C), 125.5, 129.1 (2C), 131.6 (2C), 135.1, 137.8, 147.7, 153.8, 163.2; minor diastereoisomer: δ_C 16.5, 20.1, 41.8, 44.8, 110.7, 111.3, 118.4 (2C), 123.9 (2C), 125.5, 129.2 (2C), 131.8 (2C), 135.2, 137.7, 148.1, 151.3, 164.9. Anal. for a mixture: Calcd for $C_{20}H_{13}N_5O_3$: C, 64.69; H, 3.53; N, 18.86. Found: C, 64.51; H, 3.48; N, 18.69.

(2*R,3*S**)-4-Methyl-7-oxo-2-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3j)** White solid; yield 1.88 g (75%); mp 194–195°C; IR: ν_{max} 3427, 3244, 2976, 2243, 1724, 1579, 1498, 1449, 1388, 1263 cm^{-1}; MS: *m/z* (%) 250 ([M]$^+$, 25), 195 (3), 185 (11), 166 (15), 148 (10), 144 (12), 119 (15), 109 (19), 92 (63), 91 (100); ^{1}H NMR: δ_H 1.55 (s, 3H, CH_3), 3.98 (s, 1H, CH), 7.43–7.49 (m, 5H, Ar), 11.96 (s, 1H, NH); ^{13}C NMR: δ_C 16.3, 18.6, 42.0, 42.7, 110.9, 111.4, 127.7, 129.0 (2C), 129.4, 129.7 (2C), 150.2, 168.6. Anal. Calcd for $C_{14}H_{10}N_4O$: C, 67.19, H, 4.03, N, 22.39. Found: C, 67.08, H, 4.12, N, 22.21.

(2*R,3*S**)-2-(4-*tert*-Butylphenyl)-4-methyl-7-oxo-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3k)** White solid; 2.02 g (66%); mp: 205–207°C; IR: ν_{max} 3459, 3104, 2966, 2254, 1717, 1589, 1391, 1308, 1268, 1203 cm^{-1}; MS: *m/z* (%) 306 ([M]$^+$, 100), 291 (79), 263 (12), 242 (27), 227 (65), 207 (41), 185 (35), 152 (19), 118 (23); ^{1}H NMR: δ_H 1.28 (s, 9H, *t*-Bu), 1.55 (s, 3H, CH_3), 3.92 (s, 1H, CH), 7.38 (d, *J* = 8.2 Hz, 2H, Ar), 7.47 (d, *J* = 8.2 Hz, 2H, Ar), 11.95 (s, 1H, NH); 13C NMR: δ_C 16.3, 18.5, 30.9 (3C), 34.4, 41.7, 56.0, 110.9, 111.5, 125.6 (2C), 129.3, 129.4 (2C), 150.3, 152.0, 168.6. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57, H, 5.92, N, 18.29. Found: C, 70.43, H, 6.03, N, 18.13.

2-(4-Chlorophenyl)-4-methyl-7-oxo-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3l) White solid; yield 2.07 g (73%); diastereomeric ratio 4:1; mp 186–188°C; (Lit. mp 184–185°C [26]); ^{1}H NMR: major diastereoisomer: δ_H 1.57 (s, 3H, CH_3), 3.95 (s, 1H, CH), 7.51–7.58 (m, 4H, Ar), 11.96 (s, 1H, NH); minor diastereoisomer: δ_H 2.13 (s, 3H, CH_3), 4.75 (s, 1H, CH), 7.38–7.47 (m, 4H, Ar), 11.76 (s, 1H, NH).

2-(3-Bromophenyl)-4-methyl-7-oxo-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (3m) White solid; yield 2.67 g (81%); diastereomeric ratio 3:1; mp 215–217°C (Lit. mp 213–214°C [23]); ^{1}H NMR: major diastereoisomer: δ_H 1.57 (s, 3H, CH_3), 3.97 (s, 1H, CH), 7.39–7.44 (m, 1H, Ar), 7.52 (d, *J* = 7.7 Hz, 1H, Ar), 7.66 (d, *J* = 7.7 Hz, 1H, Ar), 7.87 (s, 1H, Ar), 11.96 (s, 1H, NH); minor diastereoisomer: δ_H 2.13 (s, 3H, CH_3), 4.74 (s, 1H, CH), 7.32–7.38 (m, 2H, Ar), 7.49–7.51 (m, 1H, Ar), 7.58 (d, *J* = 7.5 Hz, 1H, Ar), 11.77 (s, 1H, NH).

Methyl (1*S,2*R**,3*R**)-1-cyano-4-methyl-7-oxo-2-phenyl-5,6-diazaspiro[2.4]-hept-4-ene-1-carboxylate (3n)** White solid; yield 1.78 g (63%); mp 170–172°C (Lit. [23] mp 170–171°C); ^{1}H NMR: δ_H 1.51 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.93 (s, 1H, CH), 7.42–7.46 (m, 5H, Ar), 11.87 (s, 1H, NH).

Methyl (1*S,2*R**,3*R**)-2-(4-chlorophenyl)-1-cyano-4-methyl-7-oxo-5,6-diazaspiro[2.4]-hept-4-ene-1-carboxylate (3o)** White solid; yield 2.07 g (65%); mp 148–149°C (Lit. [23] mp 148–149°C); ^{1}H NMR: δ_H 1.90 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.44 (s, 1H, CH), 7.34 (d, J = 8.4 Hz, 2H, Ar), 7.44 (d, J = 8.4 Hz, 2H, Ar), 11.70 (s, 1H, NH).

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