JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

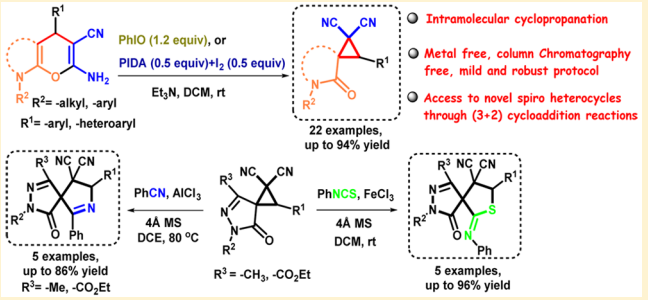
Spirocyclopropanes from Intramolecular Cyclopropanation of Pyranopyrazoles and Pyranopyrimidine-diones and Lewis Acid Mediated (3 + 2) Cycloadditions of Spirocyclopropylpyrazolones

Prasun Mukherjee and Asish R. Das*

Department of Chemistry, University of Calcutta, Kolkata-700009, India

Supporting Information

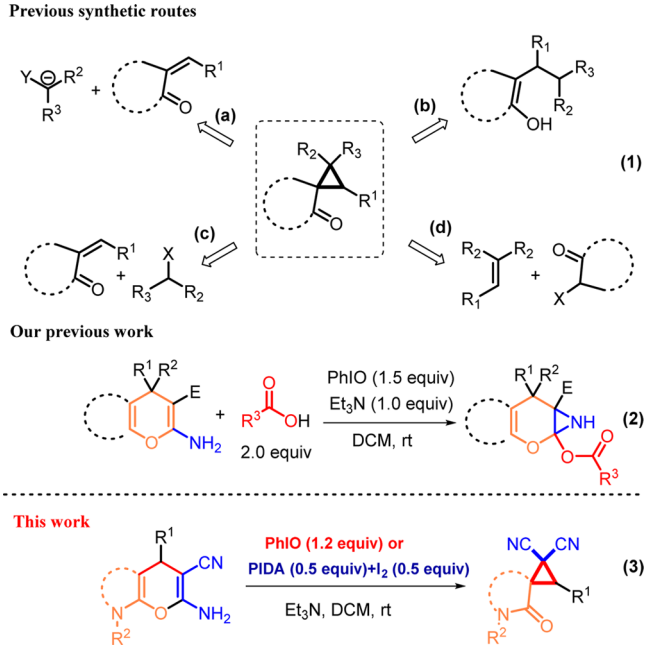
ABSTRACT: A robust intramolecular cyclopropanation reaction was first performed on pyranopyrazole and pyranopyrimidine-dione derivatives to obtain spirocyclopropylpyrazolones and barbiturates, using iodosylbenzene (PhIO) or the combination of iodobenzene diacetate (PIDA)/molecular iodine (I_2), under mild reaction conditions. Syntheses of functionally and stereochemically diversified, novel spiropyrazolone fused 2-iminothiophene and spiropyrazolone fused pyrroline scaffolds were also demonstrated via Lewis acid catalyzed highly diastereoselective (3 + 2) cycloaddition reactions of the synthesized spiro-cyclopropyl pyrazolones with phenyl isothiocyanate and benzonitrile, respectively.



The spirocyclopropyl functionality is the key structural motif in several natural products and synthetic compounds of prevalent biological and medicinal activities.[1] In addition, spirocyclopropanes are essential in organic synthesis due to their affinity toward several transformations.[2] In particular, donor−acceptor (D-A) cyclopropanes and their spiro-analogues have been proficiently exploited to synthesize numerous valuable heterocycles through countless cycloaddition reactions.[3] In this context, synthesis of functionalized spirocyclopropylbarbiturates and pyrazolones will be worthwhile, since pyrazolone and barbituric acid derivatives along with their spiro-equivalents have been well recognized for their extensive use in medicinal and pharmacological fields.[4] Also, a number of spirocyclopropylpyrazolones have been established as antifungal agents[5] and advanced AGE formation inhibitors.[6] Considering their biological and synthetic utilities,[5b,7] several synthetic routes have been developed to synthesize them, such as reaction of Michael acceptors with ylids (Scheme 1, 1a),[8] electrocatalytic cyclopropanation (Scheme 1, 1b),[9] and reaction of Michael acceptors with α-halo active methylene compounds (Scheme 1, 1c and 1d).[5b,10] However, an operationally simple, mild and competent strategy to access spirocyclopropylbarbiturates and pyrazolones from simple starting materials using less toxic reagents is still challenging and highly desirable.

In our previous work, we have demonstrated PhIO promoted intramolecular aziridination reaction to synthesize 2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl carboxylates from 2-aminopyrans in the presence of triethylamine (Et_3N) and several carboxylic acids (Scheme 1, entry 2).[11] Interestingly, during the investigation of the substrate scope of that reaction, unusual products were detected when pyranopyrimidine-dione **1a** and pyranopyrazole **1b** were employed as reactants.

Scheme 1. Synthetic Routes To Construct Spirocyclopropylpyrazolones and Barbiturates



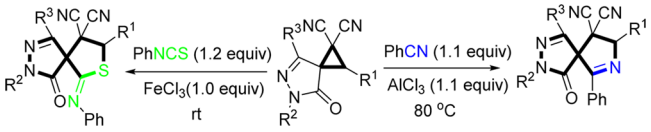
Complete characterization of those isolated products has led us to recognize them as spirocyclopropylbarbiturate and pyrazolone (**2a** and **2g**, respectively). As part of our ongoing

Received: January 20, 2017
Published: February 9, 2017

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

efforts toward the hypervalent iodine mediated synthesis of valuable heterocycles,[12] herein, we wish to disclose an unparalleled synthesis of spirocyclopropylbarbiturates and pyrazolones from their corresponding aminopyrans using PhIO or the combination of PIDA and molecular I_2 (1:1) in the presence of Et_3N at room temperature (rt) (Scheme 1, entry 1). Experimental results and literature review suggest that the oxidants used in this transformation are superior to the molecular iodine oxidants used for cyclopropanation in other systems.[13] In this present endeavor, we have also established the competency of the obtained D-A (donor−acceptor) spirocyclopropylpyrazolones toward Lewis acid catalyzed (3 + 2) cycloaddition reactions to afford functionalized novel 7-thia-2,3-diazaspiro[4.4]non-3-en-1-ones and 2,3,7-triazaspiro-[4.4]nona-3,6-dien-1-ones (Scheme 2).

Scheme 2. (3 + 2) Cycloaddition Reactions of Donor−Acceptor Spirocyclopropylpyrazolones



In order to optimize the reaction conditions, pyranopyrimidine-dione **1a** was synthesized using a known method,[14] and 1.0 equiv of **1a** was then reacted with several iodine oxidants in the presence of Et_3N using dichloromethane (DCM) as the solvent at rt.[15] After investigating several conditions, best results were obtained when the reaction was performed in the presence of PhIO (1.2 equiv) and Et_3N (1.0 equiv) in DCM (**Method A**) as well as in the presence of PIDA (0.5 equiv), I_2 (0.5 equiv), and Et_3N (2.0 equiv) in DCM (**Method B**). To explore the scope and limitation of this protocol, a variety of pyranopyrimidine-diones and pyranopyrazoles were readily synthesized following the above-mentioned procedure.[14] The intramolecular cyclopropanation reaction was then carried out applying both Methods A and B (Table 1). Both of them proceeded smoothly on pyranopyrimidine-diones and pyranopyrazoles, producing spirocyclopropanes **2a−v** in excellent yields (Table 1, entries **2a−v**). However, spirocyclopropanes **2g−l** and **2n−p** were obtained as diastereomeric mixtures from 3-methyl-pyranopyrazoles. In contrast, the reaction proceeded in a diastereospecific manner to afford **2q−v**[16] and **2m** which is probably due to the steric effect of the carbethoxy group with R^1 in 3-carbethoxy-pyranopyrazoles and the electronic repulsion between the carbonyl "O" and thienyl "S" atoms in **1m**, respectively (Table 1).[17] The presence of thienyl and substituted aryl groups (R^1) had virtually no effect on the competency of both of these methods (Table 1, entries **2a−v**).[18] Moreover, the key advantage of Methods A and B was revealed when pure products were isolated after completion of the reaction by simply evaporating the solvent and triturating the crude mass with MeOH, followed by filtration of the resulting precipitate. All synthesized compounds were well characterized through ^1H and ^{13}C NMR, IR, HRMS, and elemental analysis data. The structural motif of the spirocyclopropanes was confirmed through X-ray crystallographic analysis of compound **2q**.[19] The special reactivity of pyranopyrazoles and pyranopyrimidine-diones toward iodine oxidants to afford cyclopropanes may be due to less electron withdrawing ability of the fused pyrazole and pyrimidine-dione scaffolds through resonance, which makes the nonbonding electrons of pyran oxygen more available for the conjugation with the enaminonitrile fragment, thereby increasing the nucleophilicity as well as the reactivity of C^3 than that of the $-NH_2$ group (Scheme 3, **1**).

A plausible mechanism for this reaction is depicted in Scheme 3. For Method A, initial electrophilic attack of PhIO to the enamine fragment of **1** generates the intermediate **I**. A rearrangement within **I** in the presence of Et_3N ruptures the pyran moiety and produces intermediate **II**, which then immediately undergoes a rapid intramolecular cyclization, involving a nucleophilic substitution reaction, to afford the spirocyclopropane **2**. In the case of Method B, the in situ formed IOAc from PIDA and I_2[20] acts as the active electrophile to generate the desired product **2** via the intermediates **III** and **IV**, following essentially the same course of reaction as for Method A.

The synthetic utility of these synthesized spirocyclopropylpyrazolones was explored by successfully transforming them into unique 7-thia-2,3-diazaspiro[4.4]non-3-en-1-one and 2,3,7-triazaspiro[4.4]nona-3,6-dien-1-one derivatives through their Lewis acid catalyzed (3 + 2) cycloaddition reaction with phenyl isothiocyanate (1.2 equiv) in the presence of $FeCl_3$ (1.0 equiv) and benzonitrile (1.1 equiv) in the presence of $AlCl_3$ (1.1 equiv), respectively.[21] These reactions have proceeded efficiently for the major as well as minor (Table 2, entry **3g**) diastereomers of the corresponding cyclopropyl pyrazolones, affording the spiro-compounds in excellent yields at a short reaction time (Tables 2 and 3). Both of these cycloaddition reactions were carried out using diastereomerically pure spirocyclopropylpyrazolones, and in all the cases, the ring-enlarged products were obtained in diastereomerically pure form, which establishes these (3 + 2) cycloaddition reactions to be highly stereospecific in nature. All of these products were well characterized, and the structural motifs of these new spiropyrazolones were established through X-ray analysis of compounds **3g** and **4q**.[22]

Literature review and X-ray analysis data for both compound **3g** and **4q** suggest that both of these (3 + 2) cycloaddition reactions follow the stereospecific intimate-ion pair mechanism with the inversion of configuration in the benzylic carbon center (Scheme 4).[23] Initial coordination of Lewis acids with carbonyl functionality of **2** results in the weakening of the C^1-C^3 bond, thereby facilitates the S_N2 attack of dipolarophiles (PhNCS and PhCN) to the C^3 center of **2**, and a subsequent 120° rotation through the C^2-C^3 bond generates intermediates **IV** and **V**, which then undergo an intramolecular cyclization reaction to afford products **3** and **5**.

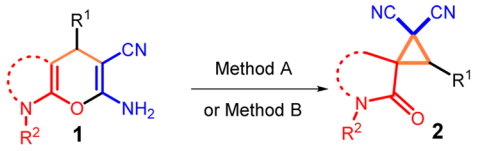
In conclusion, we have demonstrated the first example of intramolecular cyclopropanation reaction in the pyranopyrazole and pyranopyrimidine-dione system by using PhIO and PIDA/molecular I_2 combination in the presence of Et_3N at rt to synthesize biologically significant functionalized spirocyclopropylbarbiturates and pyrazolone scaffolds. The obtained spirocyclopropylpyrazolones have been efficiently transformed into novel spiropyrazolone fused 2-iminothiophene and spiropyrazolone fused pyrroline scaffolds through Lewis acid catalyzed (3 + 2) cycloaddition reactions with phenyl isothiocyanate and benzonitrile, respectively. These new types of highly functionalized spiropyrazolone heterocycles may be suitable candidates for biological and pharmacological studies.

EXPERIMENTAL SECTION

Materials and Method. ^1H NMR and ^{13}C NMR spectral analyses were carried out on 300, 75, 500, and 125 MHz instruments where

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

Table 1. Substrate Scope for the Synthesis of Spirocyclopropylbarbiturates and Pyrazolones[c]



2a A: 92% B: 94%

2b A: 88% B: 88%

2c A: 90% B: 90%

2d A: 94% B: 94%

2e A: 90% B: 92%

2f A: 92% B: 94%

2g A:90%, dr:71:29[a] B:92%, dr:71:29[a]

2h A:86%, dr:63:37[a] B: 88%, dr:63:37[a]

2i A:92%, dr:72:28[a] B: 92%, dr:72:28[a]

2j A:88%, dr:68:32[a] B: 90%, dr:68:32[a]

2k A:92%, dr:70:30[a] B:92%, dr:70:30[a]

2l A:95%, dr:86:14[b] B:96%, dr(86:14)[b]

2m A: 85% B: 86%

2n A:90%,dr:82:18[b] B: 90%,dr:82:18[b]

2o A:90%,dr:76:24[b] B:90%,dr:76:24[b]

2p A:90%,dr:70:30[b] B:92%,dr:70:30[b]

2q A: 88% B: 90%

2r A: 85% B: 85%

2s A: 88% B: 92%

2t A:86% B: 86%

2u A: 86% B: 88%

2v A: 82% B: 84%

[a]Ratio calculated from yield. [b]Ratio calculated from ^{1}H NMR. [c]**Method A**: PhIO (1.2 equiv), Et_3N (1.0 equiv), DCM (3 mL), rt. **Method B**: PIDA (0.5 equiv), I_2 (0.5 equiv), Et_3N (2.0 equiv), DCM, rt.

tetramethylsilane (TMS) was used as internal standard. Infrared spectra were recorded in KBr pellets in reflection mode on an FTIR spectrophotometer. HRMS analysis was performed on an ESI - TOF mass analyzer. Elemental analyses were done using an autoanalyzer. Suitable single crystals of compounds **2q**, **3g**, and **4q** were mounted on an X-ray diffractometer equipped with a graphite monochromator. All the reactions were monitored by thin layer chromatography carried out on aluminum-blocked silica gel plates coated with silica gel G

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

Scheme 3. Plausible Mechanism for the Intramolecular Cyclopropanation Reaction

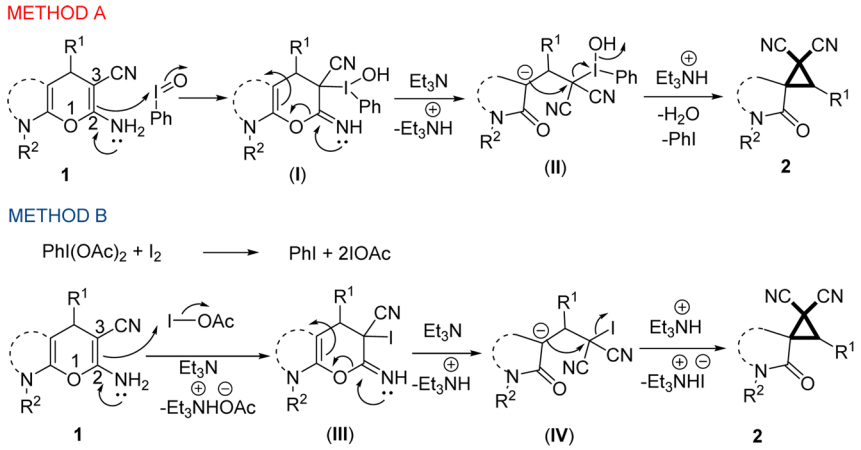
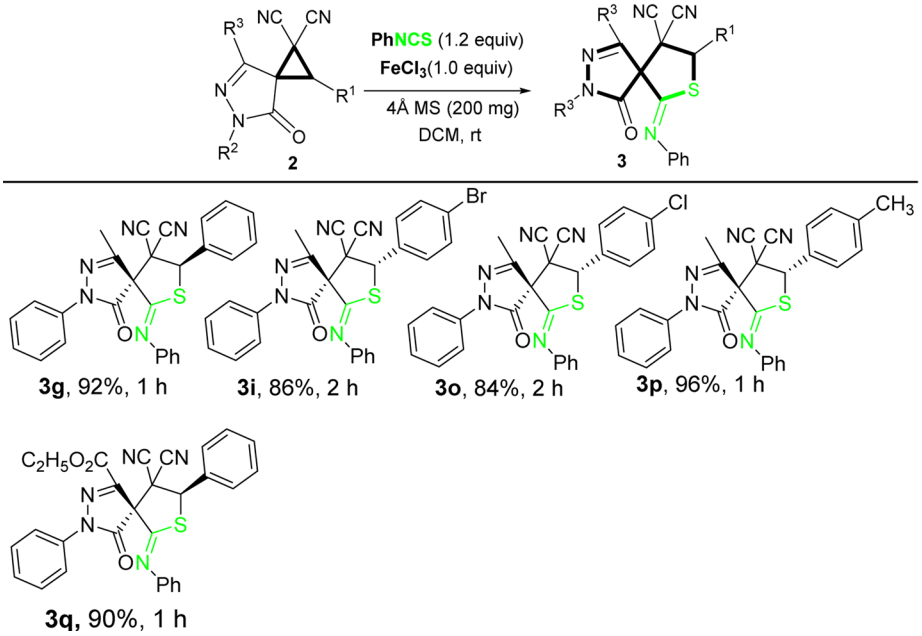


Table 2. Synthesis of Spiropyrazolone Fused 2-Iminothiophene Derivatives[a]



[a]Reaction conditions: **2** (1.0 mmol), PhNCS (1.2 mmol), $FeCl_3$ (1.0 mmol), 4 Å MS (200 mg), DCM (3 mL), rt.

under UV light and also by exposure to iodine vapor for detection. Melting points were recorded on a Köfler Block apparatus and are uncorrected. Synthetic grade chemicals from available companies were used for carrying out the organic reactions. For column chromatography, 100−200 mesh silica gel was used. All the organic solvents, used in the reaction, were appropriately dried and distilled prior to use.

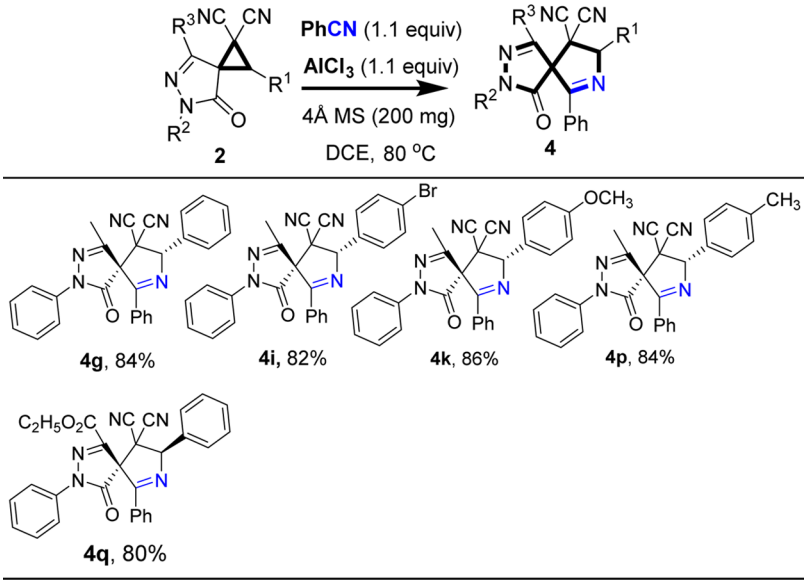
General Procedure for the Synthesis of Required Pyrazolone Derivatives. Sodium acetate (328 mg, 4.0 mmol) was added in a suspension of aromatic hydrazine hydrochloride derivatives (4.0 mmol) in 5 mL of EtOH and 1 mL of water, and the mixture was stirred at rt for 5 min. Then, to the mixture ethyl acetoacetate (521 mg, 4.0 mmol) or diethyl acetylenedicarboxylate (681 mg, 4.0 mmol) was added, and the resultant mixture was heated to reflux for 3 h. After that, the mixture was poured dropwise onto crushed ice (50 g) with vigorous stirring, and the resulting precipitate was then filtered off and crystallized from EtOH. The obtained pyrazolone derivatives were then used for the synthesis of pyranopyrimidine-diones and pyranopyrazoles without further purification.

General Procedure for the Synthesis of Pyranopyrimidine-diones 1a−f and Pyranopyrazoles 1g−v. Triethylamine (1 drop) was added to a mixture of aromatic aldehydes (2.0 mmol), malononitrile (132 mg, 2.0 mmol), and 1,3-dimethylbarbituric acid (312 mg, 2.0 mmol) or pyrazolones (2.0 mmol) in EtOH (5 mL), and the reaction mixture was refluxed for 15 min. The precipitate that was formed after cooling the reaction mixture to room temperature was filtered off, washed with water (2 × 5 mL), and EtOH (1 × 5 mL), and finally crystallized from EtOH. The crystallized pure pyranopyrimidine-diones and pyranopyrazoles were then employed for the synthesis of spirocyclopropyl barbiturates and pyrazolones without further purification.

General Method A for the Synthesis of Spirocyclopropyl-barbiturates 2a−f and Pyrazolones 2g−v. To a stirring suspension of pyranopyrimidine-diones (1.0 mmol) or pyranopyrazoles (1.0 mmol) in DCM (3 mL) at rt, PhIO (264 mg, 1.2 mmol) was added, and the resulting mixture was stirred for 2 min at rt. Then, to it 1.0 mmol of triethylamine was added, and the reaction mixture was stirred at rt for 30 min for the complete conversion of the starting 2-aminopyrans (monitored by TLC). After that, the solvent was evaporated from the reaction mixture under reduced pressure, and the resulting crude mass was triturated with MeOH (5 mL). The solid precipitate thus obtained was then filtered off and washed with MeOH (2 × 5 mL) and finally crystallized from ethyl acetate to get the pure spirocyclopropyl derivatives. For compounds **2g−k**, the diastereoisomers were separated through column chromatography

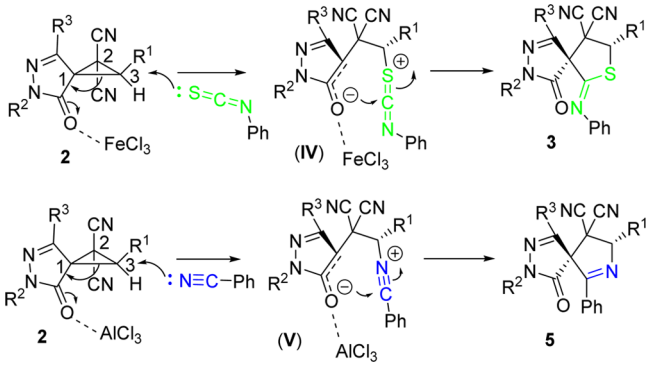
DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

Table 3. Synthesis of Spiropyrazolone Fused Pyrroline Derivatives[a]



[a]Reaction conditions: **2** (1.0 mmol), PhCN (1.1 mmol), $AlCl_3$ (1.1 mmol), 4 Å MS (200 mg), DCE (3 mL), 80 °C, 2 h.

Scheme 4. Plausible Mechanism of the (3 + 2) Cycloaddition Reactions



(silica gel 100−200 mesh) with ethyl acetate and petroleum ether (1:6−1:3, v/v) as the eluent.

General Method B for the Synthesis of Spirocyclopropyl-barbiturates 2a−f and Pyrazolones 2g−v. A mixture of PIDA (161 mg, 0.5 mmol) and I_2 (127 mg, 0.5 mmol) in DCM (3 mL) was stirred at rt for 5 min. Then, to it pyranopyrimidine-diones (1.0 mmol) or pyranopyrazoles (1.0 mmol) were added, followed by the addition of triethylamine (2.0 mmol), and the resulting mixture was stirred for 30 min at rt. After completion of the reaction (monitored by TLC), the solvent was evaporated from the reaction mixture under reduced pressure and the resulting crude mass was triturated with MeOH (5 mL). The solid precipitate thus appeared was then filtered off and washed with MeOH (2 × 5 mL) and finally crystallized from ethyl acetate to obtain the pure products. In the case of compounds **2g−k**, the diastereomers were separated through column chromatography (silica gel 100−200 mesh) with ethyl acetate and petroleum ether (1:6−1:3, v/v) as the eluent.

General Procedure for the Synthesis of 7-Thia-2,3-diaza-spiro[4.4]non-3-en-1-one Derivatives (3g, 3i, 3o, 3p, and 3q). In a 25 mL oven-dried RB fitted with a calcium chloride guard tube, some selected spirocyclopropyl pyrazolones (1.0 mmol), phenyl isothiocyanate (162 mg, 1.2 mmol), 4 Å MS (200 mg), and DCM (3 mL) were taken and stirred for 1 min. Then, to it anhydrous $FeCl_3$ (1.0 mmol) was added, and the reaction mixture was stirred at rt. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with DCM (10 mL) and filtered through a pad of Celite, and the filtrate was then subjected for column chromatography (silica gel 100−200 mesh) with ethyl acetate and petroleum ether (1:9−1:6, v/v) as the eluent to afford the pure products.

General Procedure for the Synthesis of 2,3,7-Triazaspiro-[4.4]nona-3,6-dien-1-one Derivatives (4g, 4i, 4k, 4p, and 4q). In a 25 mL oven-dried RB, some selected spirocyclopropyl pyrazolones (1.0 mmol), PhCN (114 mg, 1.1 mmol), 4 Å MS (200 mg), and DCE (3 mL) were taken and stirred at rt for 1 min under a calcium chloride guard tube. Then, to it $AlCl_3$ (147 mg, 1.1 mmol) was added, followed by the fitting of a oven-dried condenser and calcium chloride guard tube, and the mixture was then heated at 80 °C for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (10 mL) and MeOH (5 mL) and filtered through a pad of Celite, and the filtrate was then subjected for column chromatography (silica gel 100−200 mesh) with ethyl acetate and petroleum ether (1:9−1:6, v/v) as the eluent to afford the pure products.

For compounds **2a−v**, the characterization data of samples, provided by **Method B**, are documented.

5,7-Dimethyl-4,6,8-trioxo-2-phenyl-5,7-diazaspiro[2.5]-octane-1,1-dicarbonitrile (2a).[9a] White solid (Method A: 284 mg, 92%, Method B: 290 mg, 94%); mp: 258−260 °C; ^{1}H NMR (300 MHz; DMSO-d6; Me_4Si): δ 3.13 (s, 3H), 3.28 (s, 3H), 4.37 (s, 1H), 7.37 (d, J = 6 Hz, 3H), 7.46 (d, J = 6 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO-d_6; Me_4Si): δ 23.9, 29.0, 29.5, 41.8, 44.4, 111.3, 112.8, 128.6, 128.7, 129.0, 129.7, 151.3, 161.0, 163.4; IR (KBr): 3004, 2960, 2253, 1698, 1454, 1444, 1424, 1388, 1298, 752 cm^{-1}; Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.25; H, 4.00; N, 18.12.

5,7-Dimethyl-2-(4-nitrophenyl)-4,6,8-trioxo-5,7-diazaspiro-[2.5]octane-1,1-dicarbonitrile (2b).[9a] Light-yellow solid (Method A: 311 mg, 88%, Method B: 311 mg, 88%); mp: 220−222 °C; ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 3.10 (s, 3H), 3.27 (s, 3H), 4.55 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO-d_6; Me_4Si): δ 24.2, 29.1, 29.5, 41.9, 42.8, 111.0, 112.5, 123.6, 131.4, 137.0, 147.7, 151.3, 161.1, 163.0; IR (KBr): 2998, 2958, 2254, 1704, 1688, 1525, 1458, 1420, 1388, 1350, 760 cm^{-1}; Anal. Calcd for $C_{16}H_{11}N_5O_5$: C, 54.40; H, 3.14; N, 19.82. Found: C, 54.34; H, 3.20; N, 19.80.

2-(4-Cyanophenyl)-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro-[2.5]octane-1,1-dicarbonitrile (2c). Off-white solid (Method A: 300 mg, 90%, Method B: 300 mg, 90%); mp: 226−228 °C; ^{1}H NMR (500 MHz; DMSO-d_6; Me_4Si): δ 3.10 (s, 3H), 3.27 (s, 3H), 4.49 (s, 1H), 7.71 (d, J = 13.0 Hz, 2H), 7.85 (d, J = 14.0 Hz, 2H); ^{13}C{^{1}H}NMR

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

(125 MHz; DMSO-d_6; Me_4Si): δ 24.3, 29.2, 29.7, 42.0, 43.3, 111.2, 111.6, 112.7, 119.1, 131.1, 132.6, 135.1, 151.5, 161.2, 163.2; IR (KBr): 2990, 2966, 2252, 2244, 1700, 1450, 1382, 1296, 1104, 746 cm^{-1}; Anal. Calcd for $C_{17}H_{11}N_5O_3$: C, 61.26; H, 3.33; N, 21.01. Found: C, 61.20; H, 3.40; N, 20.97.

2-(4-Bromophenyl)-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile (2d). Off-white solid (Method A: 364 mg, 94%, Method B: 364 mg, 94%); mp: 240−242 °C; ^1H NMR (500 MHz; DMSO-d_6; Me_4Si): δ 3.11 (s, 3H), 3.26 (s, 3H), 4.33 (s, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz; DMSO-d_6; Me_4Si): δ 24.2, 29.2, 29.6, 41.8, 43.6, 111.3, 112.8, 122.3, 128.8, 131.7, 132.1, 151.5, 161.2, 163.4; IR (KBr): 2996, 2969, 2252, 1710, 1450, 1380, 1292, 1106, 750, 625 cm^{-1}; Anal. Calcd for $C_{16}H_{11}BrN_4O_3$: C, 49.63; H, 2.86; N, 14.47. Found: C, 49.58; H, 2.90; N, 14.41.

5,7-Dimethyl-2-(3-nitrophenyl)-4,6,8-trioxo-5,7-diazaspiro-[2.5]octane-1,1-dicarbonitrile (2e). Off-white solid (Method A: 318 mg, 90%, Method B: 325 mg, 92%); mp: 218−220 °C; ^1H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 3.1 (s, 3H), 3.30 (s, 3H), 4.51 (s, 1H), 7.70 (t, J = 7.95 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.53 (s, 1H); $^{13}C\{^1H\}$NMR (75 MHz; DMSO-d_6; Me_4Si): δ 24.1, 28.7, 29.2, 41.5, 42.0, 110.7, 112.2, 123.3, 124.8, 129.8, 131.3, 136.2, 147.6, 151.1, 160.9, 162.8; IR (KBr): 2990, 2948, 2252, 1700, 1684, 1530, 1458, 1420, 1388, 1326, 758 cm^{-1}; Anal. Calcd for $C_{16}H_{11}N_5O_5$: C, 54.40; H, 3.14; N, 19.82. Found: C, 54.34; H, 3.18; N, 19.78.

5,7-Dimethyl-4,6,8-trioxo-2-(*p*-tolyl)-5,7-diazaspiro[2.5]-octane-1,1-dicarbonitrile (2f).[9a] Light-yellow solid (Method A: 297 mg, 92%, Method B: 303 mg, 94%); mp: 184−186 °C; ^1H NMR (500 MHz; DMSO-d_6; Me_4Si): δ 2.29 (s, 3H), 3.11 (s, 3H), 3.26 (s, 3H), 4.27 (s, 1H), 7.16 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz; DMSO-d_6; Me_4Si): δ 26.1, 28.8, 33.9, 34.4, 46.7, 49.3, 116.2, 117.8, 130.8, 134.1, 134.4, 143.0, 156.2, 165.8, 168.3; IR (KBr): 2992, 2955, 2252, 1684, 1445, 1382, 1297, 1107, 748 cm^{-1}; Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.30; H, 4.42; N, 17.35.

4-Methyl-7-oxo-2,6-diphenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (2g).[9b] Off-white solid (Method A: 294 mg, 90%, Method B: 300 mg, 92%); mp: 188−190 °C; ^1H NMR of major isomer (300 MHz; $CDCl_3$; Me_4Si): δ 1.77 (s, 3H), 3.89 (s, 1H), 7.17−7.42 (m, 8H), 7.88 (d, J = 7.5 Hz, 2H); $^{13}C\{^1H\}$NMR of major isomer (75 MHz; $CDCl_3$; Me_4Si): δ 16.3, 18.3, 42.6, 42.7, 44.4, 109.2, 109.8, 118.4, 118.5, 118.53, 125.8, 126.0, 128.8, 128.84, 129.0, 129.04, 129.1, 129.2, 129.3, 129.4, 129.9, 137.0, 151.1, 163.8; ^1H NMR of minor isomer (300 MHz; $CDCl_3$; Me_4Si): δ 2.38 (s, 3H), 4.02 (s, 1H), 7.23−7.45 (m, 8H), 7.90 (d, J = 8.7 Hz, 2H); $^{13}C\{^1H\}$NMR of minor isomer (75 MHz; $CDCl_3$; Me_4Si): δ 14.0, 19.2, 40.9, 44.0, 107.3, 111.7, 118.4, 118.44, 124.9, 125.7, 128.7, 128.7, 128.9, 128.94, 129.0, 129.6, 137.1, 151.4, 161.6; IR (KBr): 3002, 2946, 2252, 1708, 1600, 1500, 1450, 1376, 1110, 836, 742 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.56; H, 4.37; N, 17.14.

4-Methyl-2-(4-nitrophenyl)-7-oxo-6-phenyl-5,6-diazaspiro-[2.4]hept-4-ene-1,1-dicarbonitrile (2h). Off-white solid (Method A: 319 mg, 86%, Method B: 327 mg, 88%); mp: 184−186 °C; ^1H NMR of major isomer (300 MHz; DMSO-d_6; Me_4Si): δ 1.71 (s, 3H), 4.34 (s, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.93 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 8.34 (d, J = 8.4 Hz, 2H); $^{13}C\{^1H\}$NMR of major isomer (75 MHz; DMSO-d_6; Me_4Si): δ 16.5, 20.2, 41.8, 44.8, 110.7, 111.4, 118.4, 123.9, 125.5, 129.1, 129.2, 131.9, 135.4, 137.9, 148.1, 151.3, 165.0; ^1H NMR of minor isomer (300 MHz; DMSO-d_6; Me_4Si): δ 2.23 (s, 3H), 5.01 (s, 1H), 7.15 (t, J = 7.05 Hz, 1H), 7.37 (t, J = 7.05 Hz, 2H), 7.71 (d, J = 8.1 Hz, 4H), 8.16 (d, J = 7.5 Hz, 2H); $^{13}C\{^1H\}$NMR of minor isomer (75 MHz; DMSO-d_6; Me_4Si): δ 14.3, 21.2, 44.7, 109.3, 112.9, 118.5, 123.5, 125.5, 129.1, 131.7, 135.2, 137.8, 147.7, 153.9, 163.2; IR (KBr): 3004, 2969, 2249, 1719, 1596, 1528, 1501, 1449, 1371, 1350, 1328, 1119, 835, 740 cm^{-1}; Anal. Calcd for $C_{20}H_{13}N_5O_3$: C, 64.69; H, 3.53; N, 18.86. Found: C, 64.62; H, 3.58; N, 18.80.

2-(4-Bromophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (2i). Off-white solid (Method A: 373 mg, 92%, Method B: 373 mg, 92%); mp: 182−184 °C; ^1H NMR of major isomer (300 MHz; $CDCl_3$; Me_4Si): δ 1.91 (s, 1H), 3.91 (s, 1H), 7.29 (d, J = 7.5 Hz, 3H), 7.48 (t, J = 7.8 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H); $^{13}C\{^1H\}$NMR of major isomer (75 MHz; $CDCl_3$; Me_4Si): δ 16.7, 18.5, 42.2, 44.5, 109.2, 109.9, 118.7, 124.7, 125.3, 126.2, 129.1, 130.8, 132.9, 137.2, 150.9, 163.8; ^1H NMR of minor isomer (300 MHz; $CDCl_3$; Me_4Si): δ 2.34 (d, J = 4.8 Hz, 3H), 3.90 (s, 1H), 7.16−7.24 (m, 3H), 7.40 (d, J = 5.7 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 6.9 Hz, 2H); $^{13}C\{^1H\}$NMR of minor isomer (75 MHz; $CDCl_3$; Me_4Si): δ 14.3, 19.4, 40.4, 44.2, 107.4, 111.8, 118.8, 124.3, 124.4, 126.2, 129.1, 131.0, 132.5, 137.3, 151.6, 161.8; IR (KBr): 2996, 2960, 2246, 1710, 1592, 1499, 1444, 1369, 1330, 1112, 840, 755, 626 cm^{-1}; Anal. Calcd for $C_{20}H_{13}BrN_4O$: C, 59.28; H, 3.23; N, 13.83. Found: C, 59.25; H, 3.27; N, 13.79.

6-(4-Chlorophenyl)-4-methyl-2-(4-nitrophenyl)-7-oxo-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (2j). Off-white solid (Method A: 357 mg, 88%, Method B: 365 mg, 90%); mp: 192−194 °C; ^1H NMR of major isomer (300 MHz; DMSO-d_6; Me_4Si): δ 1.70 (s, 3H), 4.34 (s, 3H), 7.58 (d, J = 7.5 Hz, 2H), 7.94 (d, J = 7.5 Hz, 2H), 8.00 (d, J = 7.5 Hz, 2H), 8.33 (d, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$NMR of major isomer (75 MHz; DMSO-d_6; Me_4Si): δ 16.5, 20.4, 41.9, 44.9, 108.7, 110.7, 111.3, 1119.8, 123.9, 129.2, 131.9, 135.3, 136.7, 148.1, 151.7, 165.1; ^1H NMR of minor isomer (300 MHz; DMSO-d_6; Me_4Si): δ 2.32 (s, 3H), 5.12 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 6.3 Hz, 4H), 8.24 (d, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$NMR of minor isomer (75 MHz; DMSO-d_6; Me_4Si): δ 14.3, 21.3, 44.7, 109.2, 112.8, 120.0, 123.4, 129.1 131.7, 135.1, 136.7, 147.7, 154.2, 163.3; IR (KBr): 3000, 2960, 2250, 1711, 1592, 1530, 1501, 1449, 1370, 1346, 1324, 1120, 840, 742, 706 cm^{-1}; Anal. Calcd for $C_{20}H_{12}ClN_5O_3$: C, 59.20; H, 2.98; N, 17.26. Found: C, 59.16; H, 3.01; N, 17.24.

6-(4-Methoxyphenyl)-4-methyl-2-(4-nitrophenyl)-7-oxo-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (2k). Pale yellow solid (Method A: 369 mg, 92%, Method B: 369 mg, 92%); mp: 204−206 °C; ^1H NMR of major isomer (500 MHz; DMSO-d_6; Me_4Si): δ 1.67 (s, 1H), 3.75 (s, 1H), 3.78 (s, 3H), 7.06 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H), 8.31 (d, J = 8.5 Hz, 2H); $^{13}C\{^1H\}$NMR of major isomer (125 MHz; DMSO-d_6; Me_4Si): δ 17.0, 20.6, 45.1, 55.9, 111.2, 111.9, 114.8, 118.1, 120.9, 124.4, 131.6, 132.4, 135.9, 148.6, 154.0, 157.4, 165.0; ^1H NMR of minor isomer (300 MHz; DMSO-d_6; Me_4Si): δ 2.32 (s, 3H), 3.77 (s, 3H), 5.09 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.1 Hz, 2H); $^{13}C\{^1H\}$NMR of minor isomer (75 MHz; DMSO-d_6; Me_4Si): δ 14.2, 21.0, 44.5, 55.4, 109.3, 112.9, 114.2, 120.5, 123.4, 131.1, 131.7, 135.3, 147.7, 153.5, 156.9, 162.8; ; IR (KBr): 3081, 2956, 2842, 2252, 1723, 1602, 1516, 1342, 1247, 1178, 1025, 837, 737 cm^{-1}, Anal. Calcd for $C_{21}H_{15}N_5O_4$: C, 62.84; H, 3.77; N, 17.45. Found: C, 62.81; H, 3.79; N, 17.41.

2-(4-Methoxyphenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (2l).[9b] Off-white solid (Method A: 339 mg, 95%, Method B: 342 mg, 96%); mp: 172−174 °C; ^1H NMR of major isomer (300 MHz; $CDCl_3$; Me_4Si): δ 1.90 (s, 3H), 3.87 (s, 3H), 3.93 (s, 1H), 7.01 (d, J = 8.7 Hz, 2H), 7.28−7.33 (m, 3H), 7.45−7.50 (m, 2H), 7.98 (d, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$NMR of major isomer (75 MHz; $CDCl_3$; Me_4Si): δ 16.3, 18.5, 42.5, 44.5, 55.1, 109.2, 109.9, 114.7, 117.5, 118.4, 125.8, 128.8, 130.2, 137.0, 151.2, 160.5, 163.8; IR (KBr): 3001, 2967, 2252, 1711, 1596, 1501, 1450, 1366, 1328, 1115, 840, 752 cm^{-1}; Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.75; H, 4.51; N, 15.74.

6-(4-Methoxyphenyl)-4-methyl-7-oxo-2-(thiophen-2-yl)-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile (2m). Yellow solid (Method A: 308 mg, 85%, Method B: 312 mg, 86%); mp: 188−190 °C; ^1H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 1.78 (s, 3H), 3.79 (s, 3H), 4.16 (s, 1H), 7.10 (d, J = 15.6 Hz, 3H), 7.51 (1H), 7.73−7.78 (m, 3H); $^{13}C\{^1H\}$NMR (75 MHz; DMSO-d_6; Me_4Si): δ 16.2, 20.9, 38.2, 45.3, 55.4, 110.7, 111.5, 114.3, 120.4, 127.3, 129.2, 129.3, 130.7, 131.0, 151.5, 156.9, 164.4; IR (KBr): 2996, 2960, 2246, 1700, 1592, 1552, 1480, 1321, 1248, 1180, 1012, 856, 752 cm^{-1}; Anal. Calcd for

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

$C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.94; H, 3.94; N, 15.42.

4-Methyl-2-(3-nitrophenyl)-7-oxo-6-phenyl-5,6-diazaspiro-[2.4]hept-4-ene-1,1-dicarbonitrile (2n). Off-white solid (Method A: 334 mg, 90%, Method B: 334 mg, 90%); mp: 208−210 °C; ^{1}H NMR of major isomer (300 MHz; DMSO-d_6; Me_4Si): δ 1.59 (s, 3H), 4.15 (s, 1H), 7.19 (s, 1H), 7.40−7.45 (m, 2H), 7.68−7.72 (m, 1H), 7.83 (d, J = 6.3 Hz, 2H), 8.08 (d, J = 6.6 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.66 (s, 1H); ^{13}C{^{1}H}NMR of major isomer (75 MHz; DMSO-d_6; Me_4Si): δ 16.5, 20.4, 41.4, 44.9, 110.8, 111.5, 118.3, 124.4, 125.4, 125.5, 129.2, 130.3, 130.6, 137.0, 137.9, 148.0, 151.2, 165.1; IR (KBr): 3004, 2969, 2248, 1719, 1596, 1529, 1501, 1449, 1371, 1348, 1328, 1119, 835, 744 cm^{-1}; Anal. Calcd for $C_{20}H_{13}N_5O_3$: C, 64.69; H, 3.53; N, 18.86. Found: C, 64.66; H, 3.51; N, 18.90.

2-(4-Chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diaza-spiro[2.4]hept-4-ene-1,1-dicarbonitrile (2o). Off-white solid (Method A: 325 mg, 90%, Method B: 325 mg, 90%); mp: 190−192 °C; ^{1}H NMR of major isomer (300 MHz; $CDCl_3$; Me_4Si): δ 1.81 (s, 3H), 3.85 (s, 1H), 7.19−7.42 (m, 7H), 7.87 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H}NMR of major isomer (75 MHz; $CDCl_3$; Me_4Si): δ 16.7, 18.6, 42.2, 44.6, 109.3, 109.9, 118.8, 124.8, 126.2, 129.2, 129.9, 130.0, 130.7, 136.6, 137.2, 151.0, 163.8; IR (KBr): 2996, 2959, 2254, 1720, 1596, 1501, 1449, 1370, 1328, 1119, 835, 746, 708 cm^{-1}; Anal. Calcd for $C_{20}H_{13}ClN_4O$: C, 66.58; H, 3.63; N, 15.53. Found: C, 66.56; H, 3.65; N, 15.50.

4-Methyl-7-oxo-6-phenyl-2-(*p*-tolyl)-5,6-diazaspiro[2.4]-hept-4-ene-1,1-dicarbonitrile (2p). Off-white solid (Method A: 306 mg, 90%, Method B: 313 mg, 92%); mp: 178−180 °C; ^{1}H NMR of major isomer (300 MHz; $CDCl_3$; Me_4Si): δ 1.79 (s, 3H), 2.33 (s, 3H), 3.86 (s, 1H), 7.20 (s, 5H), 7.38 (t, J = 6.9 Hz, 2H), 7.89 (d, J = 7.2 Hz, 2H); ^{13}C{^{1}H}NMR of major isomer (75 MHz; $CDCl_3$; Me_4Si): δ 16.7, 18.7, 21.3, 43.0, 44.8, 109.6, 110.2, 118.8, 123.2, 126.1, 129.1, 130.3, 137.4, 140.5, 151.6, 164.1; IR (KBr): 3004, 2969, 2249, 1719, 1596, 1501, 1449, 1371, 1328, 1119, 835, 740 cm^{-1}; Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.06; H, 4.78; N, 16.44.

Ethyl 1,1-Dicyano-7-oxo-2,6-diphenyl-5,6-diazaspiro[2.4]-hept-4-ene-4-carboxylate (2q). Off-white solid (Method A: 338 mg, 88%, Method B: 346 mg, 90%); mp: 160−162 °C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.48 (t, J = 7.05 Hz, 3H), 4.44−4.59 (m, 2H), 5.27 (s, 1H), 7.28−7.50 (m, 8H), 7.91 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; $CDCl_3$; Me_4Si): δ 13.8, 21.8, 42.0, 42.8, 62.9, 107.4, 110.9, 119.4, 119.44, 119.5, 125.0, 126.9, 128.8, 128.9, 129.0, 129.03, 129.1, 129.5, 136.3, 141.0, 158.9, 161.9; IR (KBr): 3012, 2974, 2250, 1729, 1599, 1245, 1120, 1016, 851, 740 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{22}H_{16}N_4O_3 + Na]^+$: 407.1115, found: 407.1114.

Ethyl 1,1-Dicyano-2-(4-nitrophenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-4-carboxylate (2r). Off-white solid (Method A: 365 mg, 85%, Method B: 365 mg, 85%); mp: 194−496 °C; ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 1.36 (t, J = 7.1 Hz, 3H), 4.40 (t, J = 8.0 Hz, 2H), 5.23 (s, 1H), 7.36 (t, J = 7.2 Hz, 1H), (t, J = 7.65 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO-d_6; Me_4Si): δ 14.0, 23.7, 43.3, 62.3, 109.3, 112.5, 119.9, 123.3, 126.8, 129.3, 132.0, 134.7, 137.1, 142.3, 147.7, 159.0, 163.5; IR (KBr): 3017, 2984, 2251, 1729, 1599, 1519, 1349, 1245, 1120, 1016, 851, 740 cm^{-1}; Anal. Calcd for $C_{22}H_{15}N_5O_5$: C, 61.54; H, 3.52; N, 16.31. Found: C, 61.52; H, 3.56; N, 16.28.

Ethyl 1,1-Dicyano-6-(4-methoxyphenyl)-2-(4-nitrophenyl)-7-oxo-5,6-diazaspiro[2.4]hept-4-ene-4-carboxylate (2s). White solid (Method A: 404 mg, 88%, Method B: 422 mg, 92%); mp: 210−212 °C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.41 (t, J = 7.05 Hz, 3H), 3.78 (s, 3H), 4.37−4.52 (m, 2H), 5.24 (s, 1H), 6.92 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 9.3 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; $CDCl_3$; Me_4Si): δ 14.1, 21.9, 40.8, 42.8, 55.6, 63.3, 107.5, 110.7, 114.4, 114.5, 121.7, 124.2, 129.5, 130.6, 132.4, 140.5, 148.5, 158.8, 159.3, 161.9; IR (KBr): 3027, 2986, 2254, 1723, 1604, 1516, 1437, 1349, 1249, 1126, 1019, 834, 736 cm^{-1}; Anal. Calcd for $C_{23}H_{17}N_5O_6$: C, 60.13; H, 3.73; N, 15.24. Found: C, 60.10; H, 3.76; N, 15.22.

Ethyl 1,1-Dicyano-2-(4-cyanophenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-4-carboxylate (2t). White solid (Method A: 352 mg, 86%, Method B: 352 mg, 86%); mp: 194−196 °C; ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 1.36 (t, J = 7.1 Hz, 3H), 4.34−4.47 (m, 2H), 5.20 (s, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; DMSO-d_6; Me_4Si): δ 14.0, 23.6, 43.2, 62.3, 109.3, 111.7, 112.6, 118.6, 119.9, 126.8, 129.3, 131.4, 132.2, 132.8, 137.1, 142.2, 159.0, 163.5; IR (KBr): 3015, 2982, 2254, 2242, 1715, 1600, 1245, 1120, 1016, 851, 742 cm^{-1}; Anal. Calcd for $C_{23}H_{15}N_5O_3$: C, 67.48; H, 3.69; N, 17.11. Found: C, 67.44; H, 3.74; N, 17.08.

Ethyl 1,1-Dicyano-2-(3-nitrophenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-4-carboxylate (2u). White solid (Method A: 369 mg, 86%, Method B: 378 mg, 88%); mp: 188−190 °C; ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 1.36 (t, J = 6.6 Hz, 3H), 4.35−4.43 (m, 2H), 5.21 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.4 Hz, 2H), 7.69−7.78 (m, 3H), 8.09 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.66 (s, 1H); ^{13}C{^{1}H}NMR (75 MHz; DMSO-d_6; Me_4Si): δ 14.0, 23.9, 43.3, 62.2, 109.4, 112.6, 119.8, 123.8, 125.6, 126.8, 129.4, 129.5, 129.9, 137.1, 137.3, 142.4, 147.6, 159.0, 163.6; IR (KBr): 3012, 2974, 2252, 1729, 1599, 1525, 1345, 1245, 1120, 1016, 851, 740 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{22}H_{15}N_5O_5 + Na]^+$: 452.0965, found: 452.0979.

Ethyl 1,1-Dicyano-7-oxo-6-phenyl-2-(thiophen-2-yl)-5,6-diazaspiro[2.4]hept-4-ene-4-carboxylate (2v). Yellow solid (Method A: 320 mg, 82%, Method B: 328 mg, 84%); mp: 176−178 °C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.47 (t, J = 7.1 Hz, 3H), 4.46−4.59 (m, 2H), 5.34 (s, 1H), 7.11 (t, J = 4.2 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.45−7.55 (m, 4H), 7.89 (d, J = 7.8 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; $CDCl_3$; Me_4Si): δ 14.0, 22.9, 38.2, 43.3, 63.2, 107.7, 110.8, 119.9, 126.1, 127.3, 127.6, 128.4, 129.2, 130.5, 136.5, 140.8, 159.3, 162.0; IR (KBr): 3010, 2936, 2249, 1739, 1711, 1592, 1552, 1488, 1321, 1248, 1180, 1116, 1015, 856, 754 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{20}H_{14}N_4O_3S + H]^+$: 391.0859, found: 391.0865.

(*Z*)-1-Methyl-4-oxo-3,8-diphenyl-6-(phenylimino)-7-thia-2,3-diazaspiro[4.4]non-1-ene-9,9-dicarbonitrile (3g). Off-white solid (425 mg, 92%); mp: 194−196 °C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.52 (s, 3H), 6.37 (s, 1H), 6.98 (d, J = 7.5 Hz, 2H), 7.16−7.42 (m, 9H), 7.59 (d, J = 4.8 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; $CDCl_3$; Me_4Si): δ 15.9, 29.3, 29.6, 31.9, 47.5, 54.2, 72.0, 109.8, 110.0, 119.8, 120.0, 126.6, 128.8, 129.0, 129.2, 129.4, 131.0, 136.5, 148.9, 154.0, 158.4, 165.5; IR (KBr): 3032, 2976, 2249, 1732, 1629, 1591, 1489, 1304, 1193, 1107, 1010, 760 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{27}H_{19}N_5OS + H]^+$: 462.1383, found: 462.1362.

(*Z*)-8-(4-Bromophenyl)-1-methyl-4-oxo-3-phenyl-6-(phenylimino)-7-thia-2,3-diazaspiro[4.4]non-1-ene-9,9-dicarbonitrile (3i). Off-white solid (465 mg, 86%); mp: 264−266 °C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.51 (s, 3H), 6.33 (s, 1H), 6.98 (d, J = 7.5 Hz, 2H), 6.99−7.55 (m, 10H), 7.82 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz; $CDCl_3$; Me_4Si): δ 15.9, 29.6, 30.2, 47.2, 53.6, 71.8, 109.6, 109.8, 119.8, 119.84, 119.9, 120.0, 125.6, 126.7, 126.8, 127.8, 129.1, 129.5, 130.7, 132.7, 136.5, 148.8, 153.9, 157.8, 165.3; IR (KBr): 3062, 2953, 2251, 1699, 1635, 1590, 1487, 1370, 1279, 1072, 998, 765, 620 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{27}H_{18}BrN_5OS + H]^+$: 540.0488, found: 540.0488.

(*Z*)-8-(4-Chlorophenyl)-1-methyl-4-oxo-3-phenyl-6-(phenylimino)-7-thia-2,3-diazaspiro[4.4]non-1-ene-9,9-dicarbonitrile (3o). White solid (417 mg, 84%); mp: 272−274 °C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.53 (s, 3H), 6.37 (s, 1H), 6.99 (d, J = 7.8 Hz, 2H), 7.16−7.42 (m, 8H), 7.55 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.1, 2H); ^{13}C{^{1}H}NMR (75 MHz; $CDCl_3$; Me_4Si): δ 16.0, 47.3, 53.6, 71.9, 109.7, 109.9, 119.9, 120.0, 120.1, 126.7, 126.8, 127.4, 129.2, 129.3, 129.5, 129.53, 129.8, 130.6, 136.5, 137.4, 148.9, 154.0, 157.9, 165.4; IR (KBr): 3030, 2966, 2253, 1730, 1627, 1590, 1486, 1302,

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

1200, 1110, 1008, 756, 705 cm^{-1}; Anal. Calcd for $C_{27}H_{18}ClN_5OS$: C, 65.38; H, 3.66; N, 14.12. Found: C, 65.36; H, 3.70; N, 14.08.

(*Z*)-1-Methyl-4-oxo-3-phenyl-6-(phenylimino)-8-(*p*-tolyl)-7-thia-2,3-diazaspiro[4.4]non-1-ene-9,9-dicarbonitrile (3p). Off-white solid (456 mg, 96%); mp: 222−224 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.40 (d, J = 4.5 Hz, 3H), 2.60 (d, J = 5.4 Hz, 3H), 6.43 (d, J = 4.5 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.23−7.58 (m, 10H), 7.92 (d, J = 8.1 Hz, 2H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 15.7, 21.0, 47.3, 53.8, 71.7, 109.6, 109.8, 119.5, 119.8, 125.3, 126.3, 128.8, 129.1, 129.8, 129.84, 136.3, 141.1, 148.7, 153.8, 158.4, 165.2; IR (KBr): 3030, 2954, 2251, 1705, 1636, 1593, 1493, 1369, 1277, 766, 691, 510 cm^{-1}; Anal. Calcd for $C_{28}H_{21}N_5OS$: C, 70.72; H, 4.45; N, 14.73. Found: C, 70.68; H, 4.50; N, 14.71.

Ethyl (*Z*)-9,9-Dicyano-4-oxo-3,8-diphenyl-6-(phenylimino)-7-thia-2,3-diazaspiro[4.4]non-1-ene-1-carboxylate (3q). Off-white solid (468 mg, 90%); mp: 182−184 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.41 (t, J = 7.2 Hz, 3H), 4.36−4.56 (m, 2H), 6.09 (s, 1H), 6.9675 6.98 (d, J = 8.0 Hz, 2H), 7.15−7.88 (m, 13H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 13.9, 48.0, 55.0, 62.9, 70.2, 109.4, 110.2, 119.4, 119.5, 119.8, 120.2, 120.6, 120.64, 120.7, 126.4, 127.7, 128.2, 129.0, 129.1, 129.2, 129.3, 131.0, 135.6, 145.9, 149.4, 157.5, 157.8, 166.8 ; IR (KBr): 3033, 2977, 1735, 1628, 1590, 1489, 1304, 1193, 1107, 1006, 760, 691 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{29}H_{21}N_5O_3S + H]^+$: 520.1438, found: 520.1453.

1-Methyl-4-oxo-3,6,8-triphenyl-2,3,7-triazaspiro[4.4]nona-1,6-diene-9,9-dicarbonitrile (4g). White solid (361 mg, 84%); mp: 162−164 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.22 (s, 3H), 6.49 (s, 1H), 7.23−7.89 (m, 15H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 16.9, 29.7, 50.3, 75.1, 79.7, 110.6, 111.5, 119.6, 126.8, 127.1, 127.12, 127.2, 127.3, 127.4, 127.43, 129.1, 129.2, 129.23, 129.3, 129.5, 129.54, 130.0, 130.3, 130.5, 132.9, 134.1, 136.7, 137.5, 155.1, 165.5, 166.0; IR (KBr): 3069, 2923, 2854, 2249, 1715, 1595, 1494, 1363, 1291, 1267, 1118, 757, 689 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{27}H_{19}N_5O + H]^+$: 430.1662, found: 430.1642.

8-(4-Bromophenyl)-1-methyl-4-oxo-3,6-diphenyl-2,3,7-triazaspiro[4.4]nona-1,6-diene-9,9-dicarbonitrile (4i). Off-white solid (417 mg, 82%); mp: 170−172 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.23 (s, 3H), 6.44 (s, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.36−7.62 (m, 11H), 7.87 (d, J = 8.1 Hz, 2H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 16.6, 49.7, 74.7, 78.6, 110.2, 110.9, 119.3, 119.4, 124.1, 126.6, 126.8, 128.7, 129.0, 129.2, 129.23, 130.0, 132.2, 132.8, 136.3, 154.7, 165.0, 166.2; IR (KBr): 3066, 2926, 2255, 1719, 1628, 1595, 1491, 1368, 1296, 1270, 1124, 1070, 763 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{27}H_{18}BrN_5O + H]^+$: 508.0767, found: 508.0780.

8-(4-Methoxyphenyl)-1-methyl-4-oxo-3,6-diphenyl-2,3,7-triazaspiro[4.4]nona-1,6-diene-9,9-dicarbonitrile (4k). White solid (395 mg, 86%); mp: 158−160 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.33 (s, 3H), 3.90 (s, 3H), 6.56 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.45−7.67 (m, 9H), 7.99 (d, J = 8.4 Hz, 2H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 16.6, 50.2, 55.0, 74.7, 79.3, 110.5, 111.2, 114.3, 1193, 125.6, 126.4, 126.6, 126.8, 128.4, 128.42, 129.0, 129.1, 129.3, 130.2, 132.5, 136.4, 154.8, 160.5, 165.2, 165.4; IR (KBr): 3070, 2929, 2836, 2254, 1713, 1630, 1602, 1504, 1368, 1299, 1247, 1173, 1123, 1029, 831, 765 cm^{-1}; HRMS (ESI-TOF) m/z Calcd for $[C_{28}H_{21}N_5O_2 + Na]^+$: 482.1587, found: 482.1564.

1-Methyl-4-oxo-3,6-diphenyl-8-(*p*-tolyl)-2,3,7-triazaspiro-[4.4]nona-1,6-diene-9,9-dicarbonitrile (4p). White solid (372 mg, 84%); mp: 168−170 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 2.33 (s, 3H), 2.46 (s, 3H), 6.57 (s, 1H), 7.33−7.67 (m, 12H), 7.99 (d, J = 8.4 Hz, 2H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 16.6, 21.1, 50.1, 74.7, 79.4, 110.4, 111.2, 119.3, 119.4, 126.4, 126.7, 126.8, 126.9, 128.9, 129.0, 129.1, 129.13, 129.5, 129.6, 130.2, 130.7, 132.5, 136.3, 139.7, 154.9, 165.2, 165.5; IR (KBr): 3060, 2921, 2254, 1717, 1625, 1596, 1496, 1368, 1297, 1270, 1122, 1035, 767 cm^{-1}; Anal. Calcd for $C_{28}H_{21}N_5O$: C, 75.83; H, 4.77; N, 15.79. Found: C, 75.80; H, 4.74; N, 15.82.

Ethyl 9,9-Dicyano-4-oxo-3,6,8-triphenyl-2,3,7-triazaspiro-[4.4]nona-1,6-diene-1-carboxylate (4q). Off-white solid (390 mg, 80%); mp: 160−162 °C; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.31−1.37 (m, 3H), 4.29−4.47 (m, 2H), 6.67 (d, J = 3.3 Hz, 1H), 7.29−7.55 (m, 13H), 7.85 (d, J = 8.1 Hz, 2H); $^{13}C\{^1H\}$NMR (75 MHz; $CDCl_3$; Me_4Si): δ 20.1, 56.5, 69.6, 78.2, 90.8, 114.5, 118.4, 126.2, 126.3, 133.6, 133.64, 133.7, 133.9, 135.3, 135.6, 136.2, 136.5, 138.9, 140.7, 142.2, 151.1, 165.1, 169.4, 172.1; IR (KBr): 3010, 2950, 2252, 1725, 1714, 1624, 1594, 1500, 1365, 1300, 1268, 1130, 1122, 1030, 760 cm^{-1}; Anal. Calcd for $C_{29}H_{21}N_5O_3$: C, 71.45; H, 4.34; N, 14.37. Found: C, 71.42; H, 4.36; N, 14.35.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00089.

Optimization of the reaction conditions and stereochemical course of the intramolecular cyclopropanation reaction, X-ray crystallography data of compounds **2q**, **3g**, and **4q**, and ^1H and ^{13}C NMR spectra of all compounds (PDF)

X-ray crystallography data of compound **2q** (CIF)

X-ray crystallography data of compound **3g** (CIF)

X-ray crystallography data of compound **4q** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +913323501014, +919433120265. Fax: +913323519754. E-mail: ardchem@caluniv.ac.in, ardas66@rediffmail.com.

ORCID

Asish R. Das: 0000-0001-8900-550X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support from the center of CAS-V (Synthesis and functional materials) (support offered by UGC, New Delhi) of the department of Chemistry, University of Calcutta. P.M. thanks U.G.C. New Delhi, India, for the grant of his Senior Research Fellowship. Crystallography was performed at the DST-FIST, India-funded Single Crystal Diffractometer Facility at the Department of Chemistry, University of Calcutta.

■ REFERENCES

(1) (a) Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327. (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (c) Barrett, A. G. M.; Kasdorf, K. *J. Am. Chem. Soc.* **1996**, *118*, 11030. (d) Kakiuchi, K.; Tadaki, T.; Tobe, Y.; Odaira, Y. *Chem. Lett.* **1985**, *14*, 1565−1568. (e) Richter, R.; von Reuß, S. H.; König, W. A. *Phytochemistry* **2010**, *71*, 1371−1374.

(2) (a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (c) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. (d) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794−13795. (e) Brand, C.; Rauch, G.; Zanoni, M.; Dittrich, B.; Werz, D. B. *J. Org. Chem.* **2009**, *74*, 8779−8786. (f) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013−6020.

(3) (a) Nambu, H.; Fukumoto, M.; Hirota, W.; Yakura, T. *Org. Lett.* **2014**, *16*, 4012−4015. (b) Revuelta, J.; Cicchi, S.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 5636−5642. (c) Zorn, C.; Goti, A.; Brandi, A.; Johnsen, K.; Kozhushkov, S. I.; de Meijere, A.; Goti, A. *Chem. Commun.* **1998**, 903. (d) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (e) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (f) Schneider, T. F.; Kaschel, J.; Werz, D. B.

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802

Angew. Chem., Int. Ed. **2014**, *53*, 5504−5523. (g) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314−5317.
(4) (a) Lalit, K.; Chandresh, T.; Vivek, S. *Int. J. Res. Pharm. Sci.* **2012**, *2*, 13. (b) Mariappan, G.; Sana, B. P.; Sutharson, L.; Garg, S.; Pandey, L.; Kumar, D. *J. Pharm. Res.* **2010**, *3*, 2856. (c) Kumar, P.; Nath, C.; Agarwal, J. C.; Bhargava, K. P.; Shanker, K. *Indian J. Chem.* **1983**, *22B*, 955. (d) Srivastava, A.; Kumar, V. K. *Arzneim. Forsch.* **2002**, *52*, 787. (e) Fraser, W.; Suckling, C. J.; Wood, H. G. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, *11*, 3137.
(5) (a) Devi, S.; Nayak, A.; Mittra, A. S. *J. Indian Chem. Soc.* **1984**, *61*, 640. (b) Maruoka, H.; Kashige, N.; Eishima, T.; Okabe, F.; Tanaka, R.; Fujioka, T.; Miake, F.; Yamagata, K. *J. Heterocycl. Chem.* **2008**, *45*, 1883.
(6) Itokawa, M.; Miyata, T.; Arai, M. Eur. Pat. Appl. EP 2 189 537 A1, 2010.
(7) Dorofeeva, E. O.; Elinson, M. N.; Vereshchagin, A. N.; Stepanov, N. O.; Bushmarinov, I. S.; Belyakov, P. A.; Sokolova, O. O.; Nikishin, G. I. *RSC Adv.* **2012**, *2*, 4444−4452.
(8) (a) Croce, P. D.; Pocar, D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 620−622. (b) Ren, Z.; Cao, W.; Chen, J.; Chen, Y.; Deng, H.; Shao, M.; Wu, D. *Tetrahedron* **2008**, *64*, 5156−5161.
(9) (a) Dorofeeva, E. O.; Elinson, M. N.; Vereshchagin, A. N.; Stepanov, N. O.; Bushmarinov, I. S.; Belyakov, P. A.; Sokolova, O. O.; Nikishin, G. I. *RSC Adv.* **2012**, *2*, 4444−4452. (b) Elinson, M. N.; Dorofeeva, E. O.; Vereshchagin, A. N.; Korshunov, A. D.; Egorov, M. P. *Res. Chem. Intermed.* **2016**, *42*, 2191−2200.
(10) Kawai, D.; Kawasumi, K.; Miyahara, T.; Hirashita, T.; Araki, S. *Synlett* **2008**, *2008*, 2977−2980.
(11) Mukherjee, P.; Das, A. R. *J. Org. Chem.* **2016**, *81*, 5513−5524.
(12) (a) Pal, G.; Paul, S.; Ghosh, P. P.; Das, A. R. *RSC Adv.* **2014**, *4*, 8300. (b) Mukherjee, P.; Das, A. R. *RSC Adv.* **2016**, *6*, 132−139.
(13) (a) Ye, Y.; Zheng, C.; Fan, R. *Org. Lett.* **2009**, *11*, 3156. (b) Sathishkannan, G.; Srinivasan, K. *Org. Lett.* **2011**, *13*, 6002.
(14) (a) Zhou, J.-F.; Tu, S.-J.; Zhu, H.-Q.; Zhi, S.-J. *Synth. Commun.* **2002**, *32*, 3363−3366. (b) Martin-Leon, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Chem. Res., Synop.* **1990**, *5*, 156−7.
(15) See Table S1 in the Supporting Information for the optimization of reaction conditions.
(16) The anti-relationship between the carbethoxy group and R^1 was established through X-ray analysis data of **2q**; see Figure S1 in the Supporting Information.
(17) See Scheme S1 in the Supporting Information for the stereochemical course of the intramolecular cyclopropanation reaction.
(18) Ethyl-2-cyano-3-arylacrylate, instead of the desired spirocyclopropane, was obtained when −CN was replaced by the $-CO_2Et$ in the starting aminopyrans. This may be due to the decrease in the nucleophilicity of the β carbon with respect to the $-NH_2$ group when −CN was replaced by $-CO_2Et$ in the reactant.
(19) CCDC 1521821; see Figure S1 in the Supporting Information.
(20) (a) Courtneidge, J. L.; Lusztyk, J.; Pagé, D. *Tetrahedron Lett.* **1994**, *35*, 1003−1006. (b) Boto, A.; Hernández, R.; de León, Y.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 7796−7803. (c) Fan, R.; Li, W.; Wang, B. *Org. Biomol. Chem.* **2008**, *6*, 4615−4621. (d) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209−6211.
(21) Catalytic amounts of both of these Lewis acid catalysts have resulted in the formation of the desired products in very less amount (observed by TLC).
(22) CCDC 1521822 and 1521823; see Figures S2 and S3 in the Supporting Information.
(23) (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642−8650. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014−16015.

DOI: 10.1021/acs.joc.7b00089
J. Org. Chem. 2017, 82, 2794−2802