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Stereoselective cascade assembling of benzylidenecyanoacetates and 1,3-dimethylbarbituric acid into (1*R**,2*S**)-1-cyano-5,7-dialkyl-4,6,8-trioxo-2-aryl-5,7-diazaspiro[2.5]octane-1-carboxylates

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Abstract: A new stereoselective cascade reaction of benzylidenecyanoacetates and 1,3-dimethylbarbituric acid by the action of bromine in the presence of a base into substituted (barbituric acid)-5-spirocyclopropanes is described. The yields are in the range of 60%–75%. Nuclear magnetic resonance (NMR) studies indicate that this cascade transformation results in the stereoselective formation of spiro products with *trans*-configuration of aryl and alkoxy-carbonyl substituents in the cyclopropane ring. The products are a perspective class of compounds with prominent pharmacological and physiological activity.

Keywords: barbiturates; benzylidenecyanoacetates; cascade reaction; 5,7-diazaspiro[2.5]octane-1-carboxylates; spiro.

Introduction

Cascade reactions are a powerful method to construct complex molecules from readily available starting materials by combining two or more processes into a single transformation [1, 2]. In cascade reactions, several bonds are formed by one operation that makes them useful for the creation of polycyclic and spiro compounds [3]. Thus, cascade reactions exhibit increasing importance in modern organic chemistry [4, 5].

The cyclopropane moiety is an important structural unit for many synthetic and naturally occurring compounds with an inherent wide spectrum of biological properties ranging from enzyme inhibition to herbicidal, antibiotic, antitumor and antiviral activities [6–8]. Hexahydropyrimidine-2,4,6-trione (barbituric acid) represents a type of a privileged medicinal scaffold [9, 10]. Its 5-substituted derivatives are known as barbiturates. Many barbiturates are drugs that act on the central nervous system [11, 12]. The current interest in barbiturates also arises from their pharmacological potential as analeptics, anti-AIDS agents and anticancer agents [13–15]. Many bioactive spirobarbiturates [16] show a neuropharmacological effect [17] and are inhibitors of MMP-13 [18] and dihydroorotate dehydrogenase (DHODase) [19]. Related 1-phenyl-5,7-diazaspiro[2.5]octane-4,6,8-trione [a (barbituric acid)-5-spirocyclopropane derivative] has recently been patented as TNF- α converting enzyme and matrix metalloproteinases inhibitor that has a potential utility in the treatment of various inflammatory, infectious, immunological or malignant diseases [20]. Thus, the 5,7-diazaspiro[2.5]octane system represents a prominent spiro structural motif due to the presence of cyclopropane and hexahydropyrimidine-2,4,6-trione units.

A conventional route to such (barbituric acid)-5-spirocyclopropanes involves condensation of urea and 1,1-cyclopropyldicarboxylate esters in the presence of a base [19, 20]. Yields of these reactions are modest. Moreover, requirements for dry solvents, high temperatures and application of strong bases dramatically limits the synthetic scope of this route. Another approach to (barbituric acid)-5-spirocyclopropanes utilizes direct cyclopropanation of barbituric acid derivatives including the reaction of carbenes or ylides with carbon-carbon double bond of benzylidenobarbiturates [21], base-promoted high-temperature alkylation of barbituric acid with dibromoethane [22] and condensation of acetylenic esters with

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barbituric acid in the presence of triphenylarsine [23]. Recently, *N*-iodosuccinimide was used in radical spirocyclopropanation of barbiturates with styrenes in the presence of triazabicyclodecene under white light emitting diode (LED) light irradiation [24]. A single synthesis of CHF₂-substituted (barbituric acid)-5-spirocyclopropane using α -(difluoromethyl)vinylsulfonium salt has also been reported [25].

During our studies on cascade and multicomponent reactions, we have suggested a new approach to the construction of the functionally substituted cyclopropane ring [26, 27] starting from diverse CH-acids [28–37]. Examples are chemical [38] and electrochemical [39] syntheses of 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles and 2-aryl-1-cyano-5-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1-carboxylates starting with barbiturates [39]. In continuation of our efforts on the cascade transformations of activated olefins and CH-acids and in the light of biomedical applications of (barbituric acid)-5-spirocyclopropanes, we now report a convenient and facile cascade procedure for the simple and efficient stereoselective synthesis of such derivatives by the reaction of benzylidenecyanoacetates and barbiturates.

Results and discussion

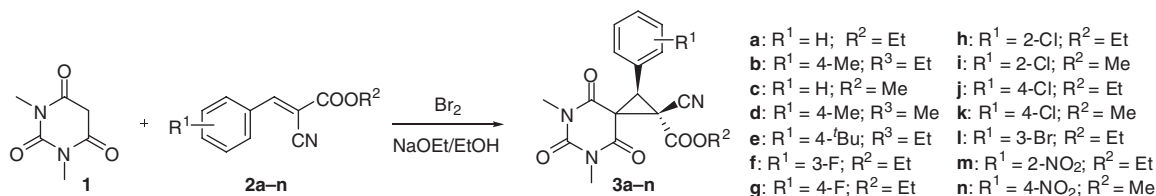
The stereoselective synthesis of (barbituric acid)-5-spirocyclopropanes **3a–n** by treatment of a mixture of 1,3-dimethylbarbituric acid (**1**) and benzylidenecyanoacetates **2a–n** with Br₂/NaOEt in ethanol is shown in Scheme 1. Initially, this cascade transformation was studied using **1** and benzylidenecyanoacetate **2a**. Under optimized conditions, substrate **1** (10 mmol) was allowed to react with compound **2a** (10 mmol) in the presence of EtONa (16 mmol) and bromine (10 mmol) in EtOH (30 mL) for 3 h. The use of either smaller or larger amount of EtONa resulted in a decreasing yield of the product **3a**. The remaining products **3b–n** were obtained in 60%–75% yields under similar conditions.

In principle, the spiro products **3a–n** can exist as a pair of diastereoisomers with *trans*- or *cis*-configuration of aryl and alkoxy carbonyl substituents in the cyclopropane ring. However, analysis of ¹H-NMR spectra of **3a–n** clearly shows the presence of a single diastereomer in each case indicating stereoselectivity of the reaction. The structure of (barbituric acid)-5-spirocyclopropane **3c** was confirmed by a single-crystal X-ray diffraction (XRD) study earlier [39]. The XRD data unambiguously supports the *trans*-configuration for **3c**, with phenyl and methoxycarbonyl substituents on different sides of the cyclopropane ring.

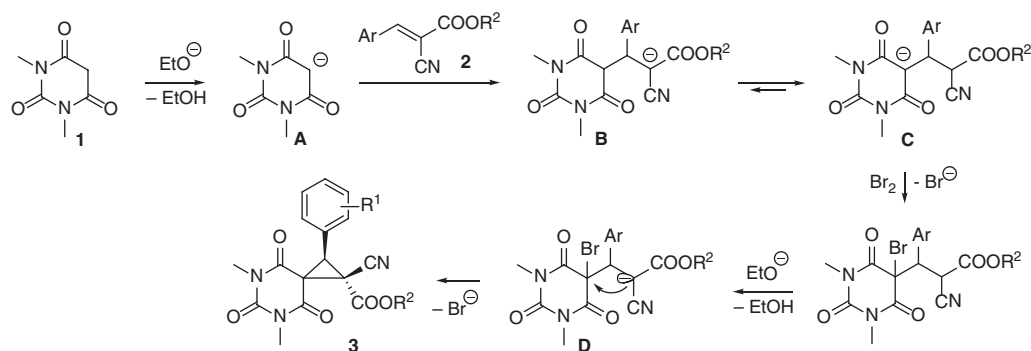
Considering these and previously reported results [40–43], the following mechanism for the cascade stereoselective synthesis of compounds **3** is proposed (Scheme 2). The first suggested step is deprotonation of barbituric acid **1** by ethoxide anion which generates anion **A**. Then, the Michael addition of the barbiturate anion **A** to benzylidenecyanoacetate **2** leads to formation of anion **B**. The anion **B** is in equilibrium with anion **C**. Bromination of the anion **C** in the presence of ethoxide ion generates anion **D** which is the direct precursor to the observed product **3**. The steric hindrance between aryl and alkoxy carbonyl substituents seems to be the driving force for the stereoselectivity of cyclization leading to a cyclopropane ring with *trans*-disposition of the aryl and alkoxy carbonyl substituents.

Conclusion

A new type of cascade one-pot reaction for the direct stereoselective formation of spirocyclopropanes from benzylidenecyanoacetates and 1,3-dimethylbarbituric acid has been developed. The procedure utilizes inexpensive reagents, is easily carried out and the work up is not complicated. Analytically pure products, (1*R**,2*S**)-1-cyano-5,7-dialkyl-4,6,8-trioxo-2-aryl-5,7-diazaspiro[2.5]octane-1-carboxylates, crystallize directly from the reaction mixture.



Scheme 1 Synthesis of compounds **3a–n**.



Scheme 2 Suggested mechanism for the formation of **3**.

Experimental

Melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $\text{DMSO}-d_6$ with a Bruker Avance II 300 spectrometer at ambient temperature. Chemical shift values are relative to Me_4Si . IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass spectra (EI, 70 eV) were obtained with a Kratos MS-30 spectrometer.

General procedure for synthesis of compound **3**

A solution of EtONa (16 mmol) in ethanol (20 mL) was added to a solution of dimethylbarbiturate **1** (10 mmol, 1.56 g) and benzylidene-cyanoacetate **2** (10 mmol) in ethanol (10 mL) during 1 min. Then Br_2 (10 mmol, 1.6 g) was added. The resulting mixture was stirred for 3 h at 20–25°C, and the white solid formed (**3**) was filtered off, washed with water (2 × 2 mL), and dried under reduced pressure to give pure product **3**.

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-phenyl-5,7-diazaspiro[2.5]octane-1-carboxylate (3a) Yield 72%; mp 186–187°C (lit. [37] mp 187°C); ^1H NMR: δ 1.25 (t, $J=7.03$ Hz, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.98 (s, 1H, CH), 4.29 (q, $J=7.03$ Hz, 2H, CH_2), 7.38–7.52 (m, 5 H, Ar).

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-methylphenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3b) Yield 65%; mp 180–182°C; IR: ν 2971, 2245, 1703, 1679, 1522, 1447, 1373, 1145, 1090 cm^{-1} ; ^1H NMR: δ 1.25 (t, $J=7.03$ Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.98 (s, 1H, CH), 4.29 (q, $J=7.03$ Hz, 2H, CH_2), 7.19 (d, $J=7.70$ Hz, 2H, Ar), 7.29 (d, $J=7.70$ Hz, 2H, Ar); ^{13}C NMR: δ 13.6, 20.6, 28.5, 28.8, 36.7, 41.0, 42.5, 63.4, 112.6, 126.4, 128.8 (4C), 137.5, 150.6, 160.8, 161.6, 164.1; MS: m/z 369 (M^+ , 4), 296 (100), 239 (6), 211 (6), 182 (23), 154 (13), 127 (8), 115 (4), 58 (2%). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.65; H, 5.12; N, 11.29.

Methyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-phenyl-5,7-diazaspiro[2.5]octane-1-carboxylate (3c) Yield 70%; mp 204–205°C (Lit. [37] mp 204°C); ^1H NMR: δ 3.10 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 4.04 (s, 1H, CH), 7.32–7.47 (m, 5H, Ar).

Methyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-methylphenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3d) Yield 62%; mp 188–189°C (lit. [37] mp 189°C); ^1H NMR: δ 2.31 (s, 3H), 3.10 (s, 3H), 3.20 (s, 3H), 3.83 (s, 3H), 3.99 (s, 1H), 7.18 (d, $J=7.91$ Hz, 2H), 7.28 (d, $J=7.91$ Hz, 2H).

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-tert-butylphenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3e) Yield 60%; mp 163–164°C; IR: ν 2964, 2904, 2224, 1752, 1688, 1456, 1376, 1264, 1092, 756 cm^{-1} ; ^1H NMR: δ 1.20–1.29 (m, 12H), 3.11 (s, 3H), 3.20 (s, 3H), 3.98 (s, 1H), 4.28 (q, $J=7.15$ Hz, 2H), 7.32 (d, $J=8.32$ Hz, 2H), 7.40 (d, $J=8.32$ Hz, 2H); ^{13}C NMR: δ 13.6, 28.6, 28.9, 31.1 (3 C), 34.4, 36.9, 41.0, 42.4, 63.5, 112.8, 125.2 (2 C), 126.4, 128.7 (2 C), 150.6, 150.7, 160.9, 161.6, 164.2; MS: m/z 411 (M^+ , 19), 339 (9), 338 (100), 300 (11), 285 (21), 242 (26), 181 (10), 84 (21), 55 (58%). Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5$: C 64.22, H 6.12, N 10.21. Found: C 64.09, H 6.01, N 10.15.

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(3-fluorophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3f) Yield 63%; mp 180–181°C; IR: ν 2974, 2249, 1753, 1737, 1702, 1678, 1449, 1374, 752 cm^{-1} ; ^1H NMR: δ 1.25 (t, $J=7.15$ Hz, 3H), 3.11 (s, 3H), 3.21 (s, 3H), 4.06 (s, 1H), 4.29 (q, $J=7.15$ Hz, 2H), 7.17–7.23 (m, 1H), 7.27–7.34 (m, 2H), 7.42–7.49 (m, 1H); ^{13}C NMR: δ 13.6, 28.6, 28.9, 36.9, 39.8, 41.3, 63.6, 112.5, 115.1 ($J^2=20.9$ Hz), 116.0 ($J^2=23.0$ Hz), 125.0, 130.3 ($J^2=8.4$ Hz), 132.2 ($J^2=8.6$ Hz), 150.7, 160.9, 161.3, 161.8 ($J^2=249.6$ Hz), 164.0; MS: m/z 373 (M^+ , 16), 329 (7), 300 (100), 262 (8), 261 (17), 219 (8), 213 (9), 186 (13), 158 (28%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{FN}_3\text{O}_5$: C 57.91, H 4.32, F 5.09 N 11.26. Found: C 57.79, H 4.29, F 5.01, N 11.15.

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-fluorophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3g) Yield 65%; mp 183–184°C; IR: ν 2969, 2248, 1754, 1738, 1703, 1679, 1452, 1376, 752 cm^{-1} ; ^1H NMR: δ 1.24 (t, $J=7.15$ Hz, 3H), 3.09 (s, 3H), 3.19 (s, 3H), 4.01 (s, 1H), 4.28 (q, $J=7.15$ Hz, 2H), 7.19–7.25 (m, 2H), 7.44–7.50 (m, 2H); ^{13}C NMR: δ 13.6, 28.6, 28.9, 37.0, 41.4, 41.6, 63.6, 112.5, 115.2 ($J^2=21.8$ Hz, 2C), 125.7, 131.2 ($J^2=8.4$ Hz, 2C), 150.7, 160.9, 161.5, 161.9 ($J^2=243.8$ Hz), 164.1; MS: m/z 373 (M^+ , 5), 329 (31), 300 (100), 261 (6), 215 (8), 186 (34), 174 (10), 158 (40), 122 (29%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{FN}_3\text{O}_5$: C 57.91, H 4.32, F 5.09, N 11.26. Found: C 57.84, H 4.27, F 5.03, N 11.17.

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(2-chlorophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3h) Yield 61%; mp 187–188°C; IR: ν 2982, 2246, 1754, 1738, 1698, 1683, 1455, 1379, 752 cm^{-1} ; ^1H NMR: δ 1.26 (t, $J=7.15$ Hz, 3H), 3.10 (s, 3H), 3.23 (s,

3H), 3.97 (s, 1H), 4.30 (q, $J=7.15$ Hz, 2H), 7.40–7.46 (m, 2H), 7.48–7.56 (m, 2H); ^{13}C NMR: δ 13.7, 28.7, 29.1, 36.9, 41.1, 41.2, 63.7, 85.1, 88.7, 112.4, 128.4, 128.6, 130.4, 133.6, 150.8, 157.4, 163.4, 163.8; MS: m/z 391 (M^+ , 1), 389 (M^+ , 3), 354 (76), 318 (48), 316 (100), 308 (24), 300 (16), 282 (17), 176 (9), 174 (21%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{ClN}_3\text{O}_5$: C 55.46, H 4.14, Cl 9.10, N 10.78. Found: C 55.32; H 4.11, Cl 9.03, N 10.69.

Methyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(2-chlorophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3i) Yield 64%; mp 288–290°C; ^1H NMR: δ 3.1 (s, 3H), 3.23 (s, 3H), 3.85 (s, 3H), 3.99 (s, 1H), 7.39–7.61 (m, 4H); ^{13}C NMR: δ 28.6, 29.1, 36.5, 41.2, 41.4, 54.5, 112.3, 127.3, 127.5, 129.4, 130.4, 130.8, 133.6, 150.5, 160.7, 161.8, 164.0; IR: ν 2959, 2253, 1755, 1681, 1440, 1379, 1226, 1145, 1095, 760 cm^{-1} ; MS: m/z 377 (M^+ , 1), 375 (M^+ , 3), 340 (58), 316 (100), 308 (18), 186 (5), 174 (35), 139 (14), 126 (5), 89 (3), 59 (32%). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_5$: C 54.34, H 3.76, Cl 9.43, N 11.18. Found: C 54.22, H 3.72, Cl 9.31, N 11.09.

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-chlorophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3j) Yield 66%; mp 177–178°C; IR: ν 2987, 2249, 1752, 1737, 1705, 1688, 1450, 1382, 753 cm^{-1} ; ^1H NMR: δ 1.25 (t, $J=7.15$ Hz, 3H), 3.10 (s, 3H), 3.20 (s, 3H), 4.04 (s, 1H), 4.29 (q, $J=7.15$ Hz, 2H), 7.42–7.55 (m, 4H); ^{13}C NMR: δ 13.6, 28.6, 28.9, 36.9, 41.0, 41.5, 63.6, 112.5, 128.4 (2C), 128.6, 130.9 (2C), 133.0, 150.7, 160.9, 161.4, 164.0; MS: m/z 391 (M^+ , 3), 389 (M^+ , 9), 318 (34), 316 (100), 235 (4), 233 (8), 204 (6), 202 (19), 190 (8), 176 (18), 174 (35), 141 (10), 139 (15%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{ClN}_3\text{O}_5$: C 55.46, H 4.14, Cl 9.10, N 10.78. Found: C 55.30, H 4.12, Cl 9.05%, N 10.71.

Methyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-chlorophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3k) Yield 62%; mp 194–195°C (lit. [37] mp 195°C); ^1H NMR: δ 3.10 (s, 3H), 3.20 (s, 3H), 3.83 (s, 3H), 4.04 (s, 1H), 7.37–7.53 (m, 4H).

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(3-bromophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3l) Yield 75%; mp 175–177°C; IR: ν 2961, 2246, 1756, 1740, 1709, 1686, 1461, 1378, 752 cm^{-1} ; ^1H NMR: δ 1.24 (t, $J=7.15$ Hz, 3H), 3.10 (s, 3H), 3.19 (s, 3H), 4.06 (s, 1H), 4.28 (q, $J=7.15$ Hz, 2H), 7.36 (t, $J=7.60$ Hz, 1H), 7.44 (d, $J=7.60$ Hz, 1H), 7.55 (d, $J=7.60$ Hz, 1H), 7.55 (s, 1H); ^{13}C NMR: δ 13.8, 27.7, 30.0, 56.4, 64.0, 84.7, 89.5, 114.1, 121.9, 125.9, 129.5, 130.9, 133.1, 136.2, 150.7, 157.5, 163.3, 165.2; MS: m/z 435 (M^+ , 5), 433 (M^+ , 5), 362 (87), 360 (100), 281 (43), 279 (41), 253 (13), 251 (23), 246 (15), 236 (22), 234 (24), 167 (23), 156 (36%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{BrN}_3\text{O}_5$: C 49.79, H 3.71, Br 18.40, N 9.68. Found: C 49.68, H 3.65, Br 18.29, N 9.56.

Methyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(2-nitrophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3m) Yield 70%; mp 266–268°C; IR: ν 2963, 2251, 1681, 1525, 1425, 1343, 1257, 1145, 1095, 751 cm^{-1} ; ^1H NMR: δ 3.02 (s, 3H), 3.25 (s, 3H), 3.87 (s, 3H), 4.42 (s, 1H), 7.71 (t, $J=7.65$ Hz, 1H), 7.81 (d, $J=8.25$ Hz, 1H), 7.89 (t, $J=7.65$ Hz, 1H), 8.16 (d, $J=7.85$ Hz, 1H); ^{13}C NMR: δ 28.6, 29.0, 37.1, 41.4, 41.8, 54.5, 112.2, 125.4, 130.3, 131.8, 134.5 (2C), 147.8, 150.4, 161.2, 161.7, 164.0; MS: m/z 340 [$\text{M}^+ - 46$ (NO_2)], 100, 308 (7), 296 (10), 220 (13), 195 (3), 163 (3), 135 (11), 91 (12), 79 (4), 59 (9%). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_7$: C 52.85, H 3.65, N 14.50. Found: C 52.71, H 3.67, N 14.37.

Ethyl (1R*,2S*)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-(4-nitrophenyl)-5,7-diazaspiro[2.5]octane-1-carboxylate (3n) Yield 72%; mp 179–181°C; IR: ν 2974, 2252, 1750, 1734, 1721, 1687, 1444, 1378, 1348, 752 cm^{-1} ; ^1H NMR: δ 1.26 (t, $J=7.15$ Hz, 3H), 3.11 (s, 3H), 3.22 (s, 3H),

4.21 (s, 1H), 4.31 (q, $J=7.15$ Hz, 2H), 7.73 (d, $J=8.44$ Hz, 2H), 8.26 (d, $J=8.44$ Hz, 2H); ^{13}C NMR: δ 13.6 (2C), 28.6, 28.9, 36.9, 40.8, 41.1, 63.7, 112.3, 123.4 (2C), 130.6 (2C), 137.2, 150.7, 161.0, 161.1, 163.7; MS: m/z 400 (M^+ , 11), 327 (100), 297 (9), 281 (8), 246 (16), 218 (17), 201 (16), 139 (10), 127 (12%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_7$: C 54.00, H 4.03, N 13.99. Found: C 53.88, H 3.99, N 13.86.

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