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Electrocatalytic cascade multicomponent assembling: stereoselective one-pot synthesis of the substituted 3-azabicyclo[3.1.0]hexane-1-carboxylate system from aldehyde, malononitrile, malonate and methanol

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ABSTRACT

Electrolysis of aromatic aldehydes, malononitrile and malonate in methanol in an undivided cell in the presence of sodium bromide–sodium methoxide as double mediatory system results in the stereoselective formation of methyl (1*R**,5*R**,6*R**) 6-substituted 5-cyano-4,4-dialkoxy-2-oxo-3-azabicyclo-[3.1.0]hexane-1-carboxylates in 50–70% yields.

1. Introduction

The discovery of new synthetic methodologies to facilitate the preparation of complex organic compounds is a pivotal focal point of research activity in the field of modern organic, bioorganic and medicinal chemistry.[1] The continual upsurge in molecular complexity and diversity in natural and biologically relevant systems urges chemists to increase the tools of their arsenal. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. In addition to the intrinsic atom economy and selectivity underlying such reactions, the MCR strategy offers significant advantages over conventional linear-type synthesis due to its flexible and convergent nature.[2] The success of combinatorial chemistry in drug discovery is considerably dependent on further advancement in heterocyclic MCR methodology and, according to current synthetic requirements, environmentally benign multicomponent procedures are particularly welcome.

The advance of electrosynthesis in the last decades has provided organic chemists with a new versatile synthetic device of great promise.[3] Despite the significant synthetic potential and ecological advantages of electrochemical methods, the practical usage of electrochemical procedures is often limited on account of its technical complexity and generally long processing times. In the course of our study on the electrochemical transformation of organic compounds,[4] we have found a new type of electrochemical transformation, namely the electrocatalytic chain transformation of organic compounds induced by the catalytic amount of electrogenerated base in an undivided cell.[5] The recent example of this type procedure found by us is the stereoselective electrocatalytic chain transformation of 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates into (1*R**,5*R**,6*R**)-6-substituted-4,4-dialkoxy-5-cyano-2-oxo-3-azabicyclo-[3.1.0]hexane-1-carboxylates **1** (Scheme 1).[6]

Using the above mentioned electrocatalytic technique, we have accomplished electrocatalytic transformation of cycloalkylidenemalononitriles and malononitriles into spirotricyclic compounds containing cyclopropane and pyrroline fragments,[7] stereoselective electrocatalytic transformations of benzylidenemalononitriles and malononirile[8] as well as arylaldehydes and malononitrile[9] into bicyclic pyrrolines, and also stereoselective electrocatalytic transformation of benzylidene- or alkilidenemalononitriles and malonate into (1*R**,5*R**,6*R**)-bicyclic pyrrolidones **1** (Scheme 1) in alcohols in the presence of sodium halide as a mediator.[10]

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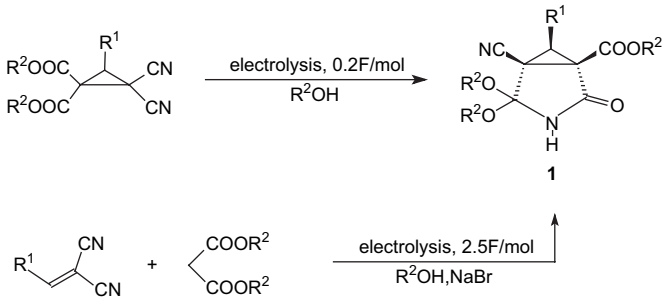


Scheme 1.

The developed unique electrochemical procedures utilize the simple equipment, an undivided cell and are valuable from the viewpoint of large-scale processes due to its catalytic nature and the use of the cheapest and environmentally responsible chemical reagent—electricity. Therefore, the implication of the described electrocatalytic methodology into a base-activated MCR concept is highly promising as it allows to combine the synthetic virtues of conventional MCR strategy with the ecological benefits and convenience of facile electrocatalytic procedure proposed.

In this way, recently we have accomplished the use of electrocatalysis in a MCR strategy. It has been proposed as a convenient and facile electrocatalytic MCR methodology for the synthesis of functionalized medicinally privileged 2-amino-4*H*-chromene scaffold based on electrochemically induced chain cyclization of cyclic 1,3-diketones, aldehydes and malononitrile,[11] or aldehydes and two different C–H acids.[4b] Under similarly electrocatalytic conditions, cyclic 1,3-diketones, isatins and malononitrile were transformed into functionalized spirocyclic (5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole system;[12] *N*-alkyl barbiturates, isatins and malononitrile were combined into functionalized spiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine] system.[13]

Other non-chain type of electrocatalytic multicomponent methodology was used for the first one-pot synthesis of a cyclopropane ring from three different molecules (Scheme 2).[14]

2. Results and discussion

In the present study, we report our results on the one-pot stereoselective multicomponent cascade transformation of five molecules of four different simple compounds into complex substituted (1*R**,5*R**,6*R**)-bicyclic pyrrolidone system **1**. This complex four component electrochemical process is combined for the first time in cascade manner electrocatalytic multicomponent assembling with electrocatalytic chain procedure (Scheme 3, Tables 1 and 2).

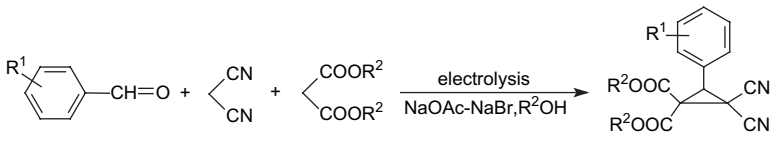
First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic transformation of benzaldehyde **2a**, malononitrile, dimethyl malonate in methanol solution in an undivided cell was studied (Table 1).

In all cases, excellent conversions of the starting compounds were obtained under 100 mA/cm^2 and after 2.5 F/mol of electricity had been passed. Under the optimal conditions (double mediatory system NaBr–NaOMe, temperature 10 °C, 2.5 F/mol passed; entry 6, Table 1), the electrolysis of arylaldehydes **2b–i**, malononitrile, dimethyl malonate in methanol in an undivided cell resulted in the formation of the corresponding bicyclic pyrrolidone system **1b–i** in 50–70% yields (Table 2).

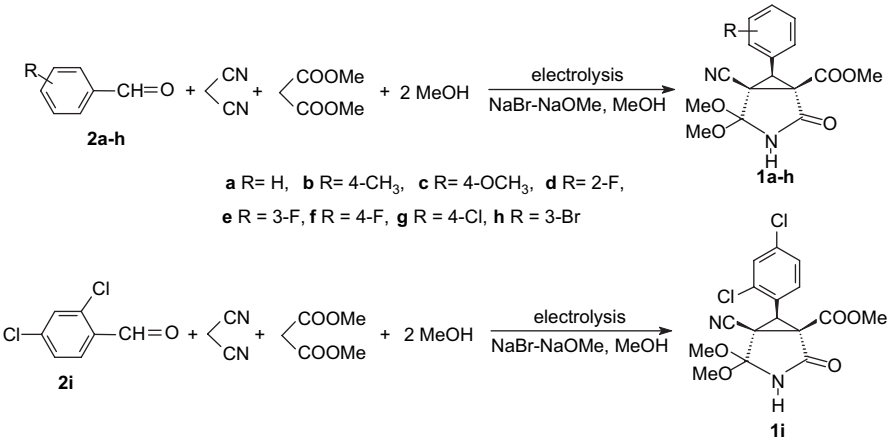
This electrochemical multicomponent cascade process takes place with high stereoselectivity. In all experiments, only one of two possible isomers of bicyclic pyrrolidones **1a–i** was found by NMR spectroscopy. The bicyclic pyrrolidone **1a** was identical to (1*R**,5*R**,6*R**)-bicyclic pyrrolidone **1a** previously obtained from benzylidenemalononitrile and dimethyl malonate,[10] the structure of which was established by single-crystal X-ray diffraction studies.[10]

Thus, in bicyclic pyrrolidone **1a** the phenyl-substituent and the pyrrolidone ring are in trans positions relative to the cyclopropane ring. By analogy and the point of view of the least steric hindrance, all other bicyclic pyrrolidones **1b–i** should have similar structures.

Taking into consideration the data obtained and our previous results on the stereoselective electrocatalytic chain transformation of 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates into



Scheme 2.



Scheme 3.

Table 1
Stereoselective cascade electrocatalytic transformation of benzaldehyde **2a**, malononitrile dimethyl malonate and methanol into bicyclic pyrrolidone **1a**[a]

N	Temperature (°C)	Mediator	Yield of **1a**[b] (%)
1	20	NaBr	10
2	10	NaBr	32
3	0	NaBr	21
4	10	NaI	20
5[d]	10	NaBr–NaOAc	37
6[e]	10	NaBr–NaOMe	71 (53)[c]

[a] Benzaldehyde (10 mmol), malononitrile (10 mmol), dimethyl malonate (10 mmol), mediator (5 mmol), methanol (20 ml), Fe cathode, C anode, current density 100 mA/cm^2, 2.5 F/mol of electricity was passed; time of the reaction: 80 min.
[b] Based on NMR spectroscopic data.
[c] In parenthesis based on the isolated bicyclic pyrrolidone.
[d] NaBr (5 mmol) and NaOAc (3 mmol).
[e] NaBr (5 mmol) and NaOMe (1 mmol).

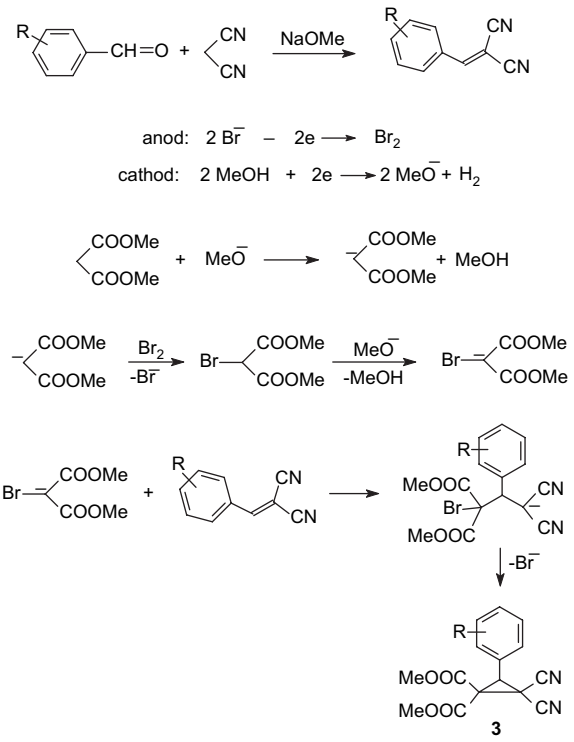
Table 2
Stereoselective electrocatalytic transformation of aldehydes **2a–i**, malononitrile, dimethyl malonate and methanol into bicyclic pyrrolidones **1a–i**[a]

Aldehyde	R	Bicyclic pyrrolidone	Yield[b] (%)
2a	H	**1a**	53
2b	4-CH_3	**1b**	55
2c	4-OCH_3	**1c**	57
2d	2-F	**1d**	64
2e	3-F	**1e**	71
2f	4-F	**1f**	56
2g	4-Cl	**1g**	49
2h	3-Br	**1h**	50
2i	2,4-Di-Cl	**1i**	52

[a] Aldehyde (10 mmol), malononitrile (10 mmol), dimethyl malonate (10 mmol), NaBr (5 mmol), NaOMe (1 mmol), methanol (20 ml), Fe cathode, C anode, current density 100 mA/cm^2, 2.5 F/mol of electricity was passed at 10 °C; time of the reaction: 80 min.
[b] Based on the isolated bicyclic pyrrolidone.

(*1R**,*5R**,*6R**)-6-substituted-4,4-dialkoxy-5-cyano-2-oxo-3-azabicyclo-[3.1.0]hexane-1-carboxylates **1** (Scheme 1),[6] and transformation of alkylidenemalononitriles and malonate into (*1R**,*5R**,*6R**)-bicyclic pyrrolidones **1** (Scheme 1)[10] and also the mechanism of electrocatalytic cyclopropane ring formation from three different molecules (Scheme 2),[14] the following reaction scheme for the stereoselective multicomponent cascade electrocatalytic transformation of aldehydes **2a–i**, malononitrile, dimethyl malonate and methanol into bicyclic pyrrolidones **1a–i** is proposed (Schemes 4 and 5).

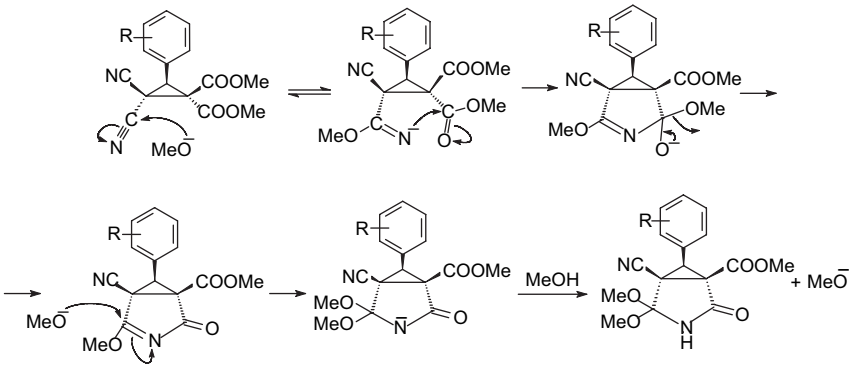
Knoevenagel condensation of malononitrile and the aldehyde is catalyzed by NaOMe (Scheme 4). The formation of bromine at the anode is a well-known process and the corresponding halogen



Scheme 4.

colour was observed at the anode when the electrolysis was conducted without stirring the reaction mixture. The deprotonation of methanol at the cathode as a result of the cathode process leads to the formation of methoxide anion. The evolution of hydrogen at the cathode is observed, especially when electrolysis is conducted without stirring of the reaction mixture. Reaction in solution between a methoxide ion and dimethyl malonate leads to the formation of a malonate anion. Bromination of the malonate anion by the bromine generated at the anode, then formation of the bromomalonate anion, followed by addition to the alkylidenemalononitrile gives rise to 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylate **3** (Scheme 4).

The stereoselective formation of **1a–i** is a result of the chain electrocatalytic mechanism shown in Scheme 5, which takes place as the successive addition of two methanol molecules to the intermediate tetracyanocyclopropane **3** initiated by methoxide ion and includes the regeneration of methoxide anion at the last stage, which continues the catalytic chain reaction process by the interaction with the next molecule of tetracyanocyclopropane (Scheme 5).



Scheme 5.

3. Conclusion

In conclusion, the simple electrocatalytic system can produce under mild conditions direct 'one-pot' stereoselective transformation of arylaldehydes, malononitrile, dimethyl malonate and methanol into bicyclic pyrrolidones **1a**–**i** in good yields. Using techniques of classical organic chemistry, this transformation could be accomplished only as a four-step process comprising (i) Knoevenagel condensation of aryl aldehyde with malononitrile with the formation of benzylidenemalononitrile,[15] (ii) bromination of malonate,[16] (iii) addition of bromomalonate to the double bond of benzylidenemalononitrile followed by cyclization,[17] and (iv) reaction of 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylate obtained in step (iii) with methoxide ions in methanol.[6] Thus, the new multicomponent electrocatalytic cascade process is the efficient and convenient stereoselective method for the synthesis of bicyclic pyrrolidones, containing cyclopropane ring—promising compounds for different biomedical applications.[18]

The procedure utilizes inexpensive reagents, simple equipment and an undivided cell; it is easily carried out and is fully beneficial from the viewpoint of ecological organic synthesis and large-scale processes.

This efficient stereoselective multicomponent electrocatalytic approach to 3-azabicyclo[3.1.0]hexane-1-carboxylate system represents a novel synthetic concept for multicomponent cascade reactions, and allows for the combination of the synthetic virtues of conventional MCRs with ecological benefits and convenience of facile electrocatalytic procedure. Therefore, this novel MCR strategy brings us a step closer to the notion of 'ideal synthesis'.[19]

4. Experimental section

4.1. General remarks

All melting points were measured with a Gallenkamp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC-300 spectrometers at ambient temperature. Chemical shifts values are relative to Me_4Si. IR spectra were registered with a SPECORD M82 spectrometer in KBr pellets. Mass spectra (EI=70 eV) were obtained directly with a Finnigan MAT INCOS 50 spectrometer.

4.2. Typical procedure

A solution of aldehyde (10 mmol), malononitrile (10 mmol), dimethyl malonate (10 mmol), sodium bromide (5 mmol) and sodium methoxide (1 mmol) in methanol (20 ml) was electrolyzed in an undivided cell equipped with C anode and Fe cathode (square of the electrodes: 5 cm^2), thermometer, external cooling and a magnetic stirrer under constant current density of 100 mA/cm^2 at 10 °C. At the end of the electrolysis, when 2.5 F/mol electricity was passed (time of the reaction: 80 min), bicyclic pyrrolidones were usually crystallized directly from the reaction mixture and were then filtered off. Additional portion of bicyclic pyrrolidones was isolated from the residue of the reaction mixture according to the following procedure. The solvent was removed and the residue was extracted with chloroform, washed with water, and dried over Na_2SO_4. Chloroform was removed and the residue was crystallized from methanol.

All compounds (**2a**–**i**) gave expected NMR spectra. For new compounds (**2e**,**f**,**h**,**i**), satisfactory elemental analyses, mass spectrometry and IR spectroscopy data were obtained.

4.2.1. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-2-oxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2a**)*

White solid. Yield 1.67 g (53%); mp 110–112 °C; lit. mp[2] 110–112 °C; δ_H (300 MHz, $CDCl_3$) 3.29 (s, 1H, CH), 3.46 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 7.35 (s, 1H, NH), 7.40 (m, 5H, C_6H_5).

4.2.2. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(4-methylphenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2b**)*

White solid. Yield 1.82 g (55%); mp 127–129 °C; lit. mp[10] 127–129 °C; δ_H (300 MHz, $CDCl_3$) 2.34 (s, 3H, CH_3), 3.25 (s, 1H, CH), 3.47 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 7.20 (d, 2H, *J* 8.0 Hz, Ar), 7.38 (d, 2H, *J* 8.0 Hz, Ar), 7.64 (s, 1H, NH).

4.2.3. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(4-methoxyphenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2c**)*

White solid. Yield 1.97 g (57%); mp 146–147 °C; lit. mp[10] 146–147 °C; δ_H (300 MHz, $CDCl_3$) 3.20 (s, 1H, CH), 3.43 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.88 (d, 2H, *J* 8.0 Hz, Ar), 7.31 (d, 2H, *J* 8.0 Hz, Ar), 7.77 (s, 1H, NH).

4.2.4. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(2-fluorophenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2d**)*

White solid. Yield 2.14 g (64%); mp 160–162 °C; lit. mp[6] 160–162 °C; δ_H (300 MHz, DMSO-d_6) 3.32 (s, 1H, CH), 3.33 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 7.25–7.45 (m, 4H, Ar), 9.80 (s, 1H, NH).

4.2.5. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(3-fluorophenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2e**)*

White solid. Yield 2.37 g (71%); mp 136–137 °C; δ_H (300 MHz, $CDCl_3$) 3.23 (s, 1H, CH), 3.47 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 7.02–7.23 (m, 3H), 7.31–7.42 (m, 1H, Ar), 7.75 (s, 1H, NH); δ_C (75 MHz, $CDCl_3$) 31.6, 38.8, 43.5, 50.1, 51.7, 53.2, 106.5, 112.4, 116.0 (d, $^2J_{CF}$ 22.8 Hz), 116.1 (d, $^2J_{CF}$ 21.4 Hz), 124.3 (d, $^4J_{CF}$ 3.0 Hz), 130.5 (d, $^3J_{CF}$ 8.7 Hz), 131.6 (d, $^3J_{CF}$ 8.8 Hz), 161.6, 162.7 (d, $^1J_{CF}$ 247.6 Hz), 166.7; MS *m*/*z* (%): 334 (4) $[M]^+$, 302 (9), 245 (10), 215 (12), 158 (71), 139 (100), 59 (83); IR (KBr): ν_{max} 2260, 1752, 1728 cm^{-1}. Anal. Calcd for $C_{16}H_{15}FN_2O_5$ (%): C, 57.49; H, 4.52; F, 5.68; N, 8.38. Found (%): C, 57.31; H, 4.62; F, 5.39; N, 8.45.

4.2.6. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(4-fluorophenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2f**)*

White solid. Yield 1.87 g (56%); mp 180–181 °C; δ_H (300 MHz, $CDCl_3$) 3.32 (s, 1H, CH), 3.48 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 7.09 (t, 2H, *J* 8.9 Hz, Ar), 7.24 (s, 1H, NH), 7.41 (dd, 2H, ^1J 8.7 Hz, ^2J 8.1 Hz, Ar); δ_C (75 MHz, $CDCl_3$) 31.7, 38.9, 43.7, 50.2, 51.8, 53.2, 106.5, 112.7, 116.0 (d, $^2J_{CF}$ 22.0 Hz), 125.0 (d, $^4J_{CF}$ 3.1 Hz), 130.6 (d, $^3J_{CF}$ 8.8 Hz), 162.9 (d, $^1J_{CF}$ 249.0 Hz), 161.5, 164.47; MS *m*/*z* (%): 334 (4) $[M]^+$, 302 (10), 245 (22), 215 (14), 158 (71), 139 (100), 59 (73); IR (KBr): ν_{max} 2248, 1760, 1728 cm^{-1}. Anal. Calcd for $C_{16}H_{15}FN_2O_5$ (%): C, 57.49; H, 4.52; F, 5.68; N, 8.38. Found (%): C, 57.24; H, 4.63; F, 5.52; N, 8.23.

4.2.7. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(4-chlorophenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2g**)*

White solid. Yield 1.72 g (49%); mp 130–132 °C; lit. mp[6] 130–132 °C; δ_H (300 MHz, $CDCl_3$) 3.21 (s, 1H, CH), 3.47 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 7.34–7.42 (m, 4H, Ar), 7.38 (s, 1H, NH).

4.2.8. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(3-bromophenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2h**)*

White solid. Yield 1.98 g (50%); mp 134–135 °C; δ_H (300 MHz, $CDCl_3$) 3.22 (s, 1H, CH), 3.49 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 7.22–7.42 (m, 3H, Ar, NH), 7.48–7.60 (m, 2H, Ar); δ_C (75 MHz, $CDCl_3$) 31.4, 38.5, 43.3, 50.0, 51.7, 53.1, 106.3, 112.3, 122.6, 126.9, 130.3, 131.2, 131.9, 132.0, 161.3, 166.03; MS *m*/*z* (%): 396 (0.6) $[M]^+$, 394 (0.7) $[M]^+$, 364 (3), 362 (3), 321 (7), 319 (7), 201 (46), 199 (48), 167 (18), 139 (40), 59 (100); IR (KBr): ν_{max} 2252, 1760, 1728 cm^{-1}. Anal. Calcd for $C_{16}H_{15}BrN_2O_5$ (%): C, 48.63; H, 3.83; Br, 20.22; N, 7.09. Found (%): C, 48.52; H, 4.01; Br, 20.07; N, 7.05.

4.2.9. Methyl (1R,5R*,6R*) 5-cyano-4,4-dimethoxy-6-(2,4-dichlorophenyl)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (**2i**)*

White solid. Yield 2.01 g (52%); mp 155–156 °C; δ_H (300 MHz, $CDCl_3$) 3.19 (s, 1H, CH), 3.46 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 7.33 (dd, 1H, ^1J 8.3 Hz, ^2J 2.1 Hz, Ar), 7.38 (s, 1H, NH), 7.46 (d, 1H, J 2.1 Hz, Ar), 7.63 (d, 1H, J 8.3 Hz, Ar); δ_C (75 MHz, $CDCl_3$) 32.7, 37.7, 42.6, 50.2, 51.9, 53.3, 106.5, 112.4, 126.6, 127.5, 129.7, 129.8, 135.5, 136.3, 162.1, 166.4; MS m/z (%): 385 (0.3) $[M]^+$, 353 (1), 319 (5), 317 (19), 259 (10), 210 (15), 208 (23), 191 (22), 189 (37), 59 (100); IR (KBr): ν_{max} 2252, 1744, 1728 cm^{-1}. Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_5$ (%): C, 49.89; H, 3.66; N, 7.27. Found (%): C, 49.75; H, 3.69; N, 7.11.

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