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# Pyridinium bromide as a mediator in electrochemical reactions: the preparation of cyclopropane-1,1-dicarbonitriles

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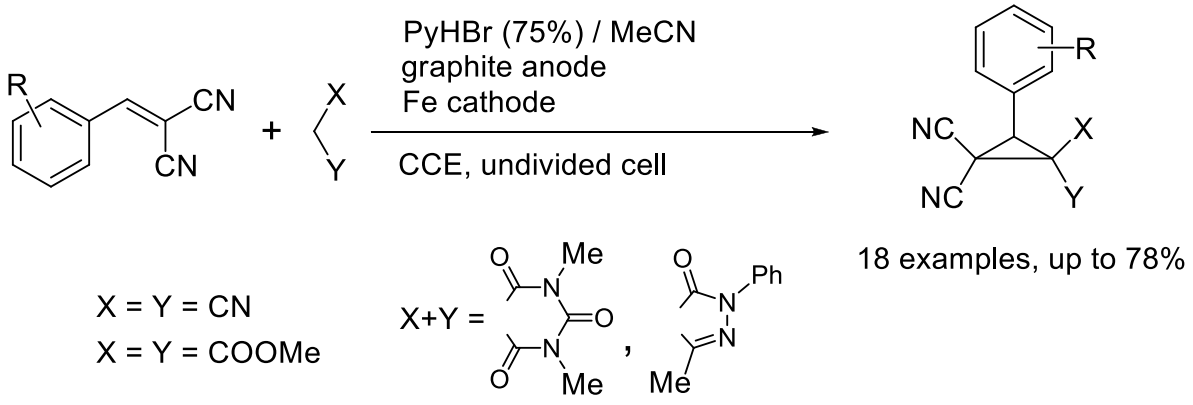
## Abstract

Pyridinium bromide has been tested as a new mediator for electrochemical transformations in methanol and acetonitrile. An efficient protocol for the synthesis of cyclopropanes *via* the electrochemical transformations of alkylidenemalononitriles and C-H acids (malononitrile, malonic ester, *N*,*N*-dimethylbarbituric acid, pyrazolin-5-ones) has been developed. The chemistry proceeds in a simple undivided cell under constant current conditions employing a substoichiometric amount of PyHBr that serves both as a redox catalyst and a supporting electrolyte; in this manner additional conducting salt is not required.




**Keywords:** Electrosynthesis, mediators, pyridinium bromide, C-H acids, cyclopropanes

## Introduction

Electrosynthesis is a competitive method in modern organic chemistry.[1-4] The importance of electrochemical synthesis lies in its great and, in some cases, unique possibilities for performing various transformations of organic compounds.[5]

In recent decades, indirect electrooxidation of organic compounds has been the subject of intensive studies.[6,7] Halides are popular inorganic mediators.[8-10] Their advantages include accessibility and low cost, as well as the fact that the majority of the processes catalyzed by these mediators are performed in an undivided cell.

C-H acids are convenient synthons for the preparation of different classes of compounds by indirect electrooxidation in the presence of alkali halides as mediators. Electrochemical transformations involving different types of C-H acids were studied. These processes are carried out in an undivided cell at constant current. Electrolysis of malononitrile or malonic esters in alcohols affords cyclopropanes.[11,12] Multicomponent transformations of malonic acid derivatives using electrolysis media lead to the stereoselective formation of polysubstituted three-carbon rings.[13-15] Cross-dehydrogenative coupling of β-diketones or β-ketoesters (C-H reagents) with carboxylic acids (O-H reagents) results in selective formation of intermolecular C-O coupling products.[16] Cyclic β-diketones enter into electrochemically induced multicomponent reactions with formation of pyrans[17,18] and furans.[19]

Electrochemical processes involving heterocyclic C-H acids are of considerable interest, since they allow the synthesis of a various types of heterocyclic compounds with a wide range of biological and pharmaceutical properties.[20] The 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones, also called barbiturates (derivatives of barbituric acid), are a well-known class of drugs that act as central nervous system depressants, and by virtue of this, they produce a wide spectrum of effects, ranging from mild sedation to anaesthesia.[21,22] An electrochemical strategy for the synthesis of pyrano[2,3-*d*]pyrimidine-2,4,7-triones is described, using an electrogenerated anion of barbituric acid in a one-pot, three component condensation of an aromatic aldehyde, Meldrum's acid (one more heterocyclic C-H acid) and barbituric acid in ethanol in an undivided cell and in the presence of sodium bromide.[23]

Among 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetriones, spirobarbiturates are a particular class of compounds with pronounced pharmacological and physiological activity.[24-26] Our previous work described the indirect electrocatalytic transformation involving barbituric acids with formation of spiro compounds: furo[2,3-*d*]-pyrimidines,[27] terpyrimidines[28] and spirobicycles containing cyclopropane and pyrimidine fragments.[29] A spirocyclopropyl moiety joined to a heterocyclic ring has attracted particular attention due to a wide number of pronounced pharmacological applications.[30,31]

Pyrazolones are another important class of heterocycles possessing important biological properties.[32] The C-H acid 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone) is a neuroprotective agent.[33] The indirect electrooxidation of edavarone and analogues in the presence of sodium halides as mediators in alcohols has been described. Thus, Zeng *et al.* have carried out dehydrodimerization and dehydrotrimerization of pyrazol-5-ones.[34] Electrolysis of edavarone with aromatic aldehydes leads to the formation of 4,10-dimethyl-2,8,11-triphenyl-2,3,8,9-tetraazadispiro[4.0.4.1]undeca-3,9-diene-1,7-diones,[35] which was recently patented as an advanced glycation end product (AGE) formation inhibitor intended for treatment of human schizophrenia.[36]

Despite the advantages and significant achievements described, the use of alkali metal halides as a mediator in alcohol solutions for carrying out electrochemical transformations of organic compounds has several disadvantages. Thus, the need to use methanol or ethanol as a solvent does not allow the transformation of organic compounds which are insoluble or poorly soluble in alcohol, which limits the choice

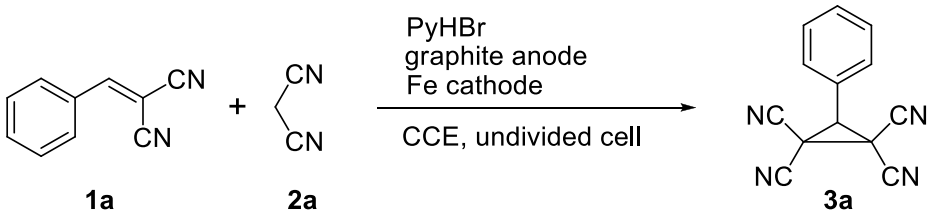
of the starting compounds and narrows the scope of the application of the electrocatalytic methodology. Further, there are also significant limitations due to the occurrence of a number of side reactions. Thus, the co-electrolysis of cyclohexylidenemalononitrile and malononitrile in ethanol in the presence of sodium bromide results in formation of the expected tetracyanocyclopropane with a tricyclic pyrroline as a side product.[37] This result is a consequence of the ethoxide attack on the cyano-groups of the cyclopropane. To avoid this side reaction, it is necessary to use an aprotic solvent such as acetonitrile, dimethylformamide or dimethylsulfoxide. However, sodium halides do not dissolve in these solvents.

As is well known, quaternary ammonium salts are widely used in electrochemistry as supporting electrolytes. Recently Little, Zeng *et al*. reported the development of an electrochemically initiated oxidative amination of benzoxazoles[38] and sulfonamides[39] using tetraalkylammonium halides and ammonium iodide as redox catalysts, respectively.

Now we present pyridinium bromide as a new mediator in electrochemical transformations involving benzylidenemalononitriles and C-H acids.

## Results and Discussion

We started using benzylidenemalononitrile **1a** and malononitrile **2a** as model substrates and performed a constant current electrolysis at 100 mA/cm$^2$ in an undivided cell, using a graphite rod (area 5 cm$^2$) as the anode and a Fe plate (area 5 cm$^2$) as the cathode (Scheme 1, Table 1).




**Scheme 1**

Initially, we optimized the catalytic efficacy of PyHBr in methanol (entries 1-10). The current density of 50 mA cm$^{-2}$, 0.75 equivalent of PyHBr, 20 °C, 2.2 F mol$^{-1}$ were found to be the optimum conditions (entry 5). Using smaller amounts of PyHBr in the electrolysis leads to the formation of **3a** in lower yields (entries 1, 2). Apparently, this is due to the incomplete regeneration of the mediator under electrolysis conditions. Raising the current density to 100 mA cm$^{-2}$ (entry 4) or the temperature to 30 °C (entry 8) also result in a decrease of the yield, possibly due to the acceleration of undesired direct electrochemical processes leading to the oligomerization of the reactants. Low yields and incomplete conversion of starting compounds were observed when electrolysis was carried out at 10 °C (entry 7). Ethanol is a slightly less effective solvent than methanol, in view of the yield. PyHBr is soluble in aprotic solvents. Acetonitrile, DMF and DMSO were tested as solvents for electrolysis (Table 1, entries 12-14). It was found that acetonitrile is also effective in the synthesis of **3a** under electrolysis conditions (entry 12).

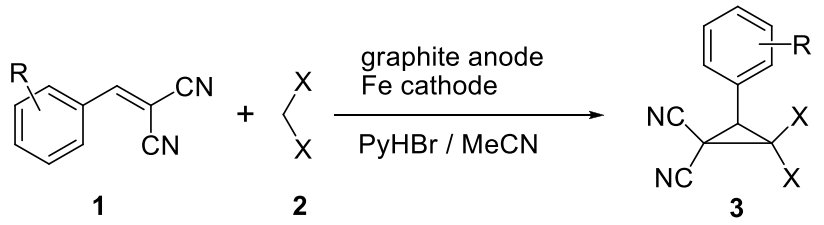
 

**Table 1.** Initial optimization of the electrochemical synthesis of tetracyanocyclopropane **3a** using PyHBr as mediator[a]

| Entry | Solvent | Equiv. of PyHBr | T/°C | Current density/ mA $cm^{-2}$ | Electricity passed/ F $mol^{-1}$ | Yield of **3a** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | MeOH | 0.3 | 20 | 100 | 2.0 | 25[c] |
| 2 | MeOH | 0.5 | 20 | 100 | 2.0 | 42 |
| 3 | MeOH | 0.75 | 20 | 100 | 2.0 | 60 |
| 4 | MeOH | 1.0 | 20 | 100 | 2.0 | 60 |
| 5 | MeOH | 0.75 | 20 | 100 | 2.2 | 68 |
| 6 | MeOH | 0.75 | 20 | 100 | 2.5 | 61 |
| 7 | MeOH | 0.75 | 10 | 100 | 2.2 | 44 |
| 8 | MeOH | 0.75 | 30 | 100 | 2.2 | 32[c] |
| 9 | MeOH | 0.75 | 20 | 50 | 2.2 | 72 |
| 10 | MeOH | 0.75 | 20 | 25 | 2.2 | 68 |
| 11 | EtOH | 0.75 | 20 | 50 | 2.2 | 62 |
| 12 | MeCN | 0.75 | 20 | 50 | 2.2 | 72 |
| 13 | DMF | 0.75 | 20 | 50 | 2.2 | 35[c] |
| 14 | DMSO | 0.75 | 20 | 50 | 2.2 | 25[c] |

[a] Benzylidenemalononitrile **1a** (10 mmol), malononitrile **2a** (10 mmol), 20 mL of solvent, undivided cell.
[b] Isolated yield. [c] NMR data.

From the results described above, we conclude that the optimal reaction conditions require using 75 mol% of PyHBr as mediator and supporting electrolyte, and 50 mA $cm^{-2}$ of current density at 20 °C. The reaction is best performed in an undivided cell using methanol or acetonitrile as the solvent without the need for additional conducting salt. It should be noted that PyHBr is an effective mediator both in methanol and in acetonitrile with a current density of 50 mA $cm^{-2}$. Previous electrochemical methods for the synthesis of tetracyanocyclopropanes **3** were carried out utilizing alkali metal halides as mediators with a current density of 100 mA $cm^{-2}$.[11] However, the existing method is only applicable in alcohols, since alkali halides are insoluble in aprotic solvents such as acetonitrile. As a result, we have now the opportunity to conduct an electrochemical reaction in a new medium.




**Scheme 2**

Under the optimal conditions, as determined above, we then studied the scope and generality of the protocol by examining reactions of benzylidenemalononitriles **1** (with both electron-withdrawing and electron-donating substituents on the aromatic ring), and with different types of C-H acids: acyclic malononitrile **2a** or

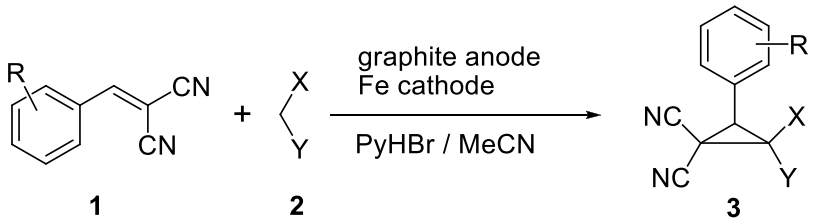
 

dimethyl malonate **2b** (Scheme 2, Table 2); heterocyclic 1,3-dimethylbarbituric acid **2c** and edavarone (3-methyl-1-phenyl-2-pyrazolin-5-one) **2d** (Scheme 3, Table 3).

**Table 2.** Electrochemical synthesis of cyclopropanes **3** using noncyclic C-H acids **2a,b** and PyHBr as mediator[a]

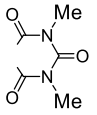
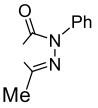
| Entry | Olefin | R | C-H acid | X | Cyclopropane | Yield of **3**, (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | H | **2a** | CN | **3a** | 72 |
| 2 | **1b** | 4-Me | **2a** | CN | **3b** | 66 |
| 3 | **1c** | 3-Br | **2a** | CN | **3c** | 58 |
| 4 | **1d** | 4-$NO_2$ | **2a** | CN | **3d** | 48 |
| 5 | **1a** | H | **2b** | COOMe | **3e** | 67 |
| 6 | **1b** | 4-Me | **2b** | COOMe | **3f** | 63 |
| 7 | **1c** | 3-Br | **2b** | COOMe | **3g** | 64 |
| 8 | **1d** | 4-$NO_2$ | **2b** | COOMe | **3h** | 38 |

[a] Benzylidenemalononitrile **1** (10 mmol), C-H acid **2** (10 mmol), 20 mL of acetonitrile, undivided cell, 20 °C, 2.2 F $mol^{-1}$, current density 50 mA $cm^{-2}$. [b] Isolated yield.




**Scheme 3**

**Table 3.** Electrochemical synthesis of cyclopropanes **3** using heterocyclic C-H acids **2c,d** and PyHBr as mediator[a]

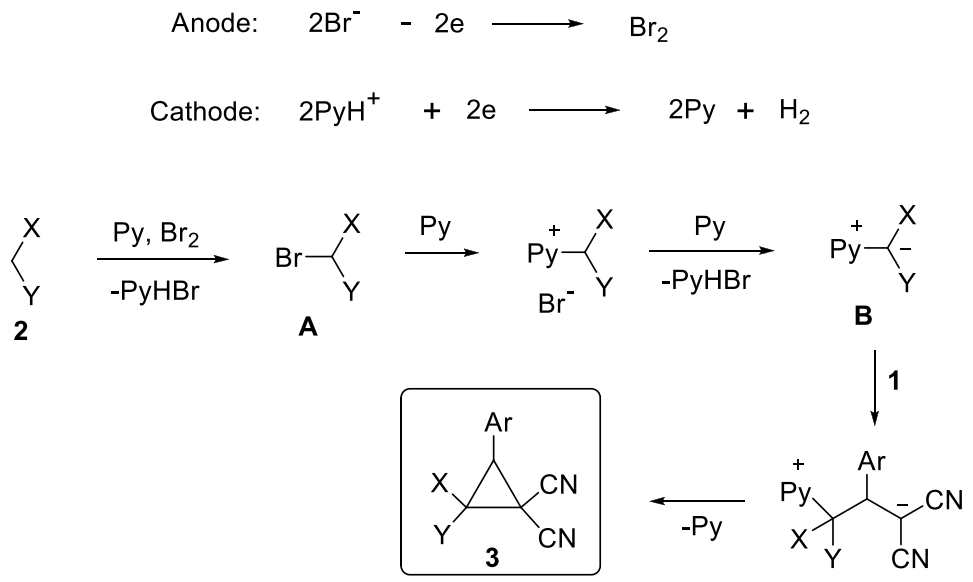
| Entry | Olefin | R | C-H acid | X+Y | Cyclopropane | Yield of **3**, (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | H | **2c** |  | **3i** | 78 |
| 2 | **1b** | 4-Me | **2c** | | **3j** | 65 |
| 3 | **1c** | 3-Br | **2c** | | **3k** | 74 |
| 4 | **1d** | 4-$NO_2$ | **2c** | | **3l** | 54 |
| 5 | **1e** | 3-OMe | **2c** | | **3m** | 66 |
| 6 | **1a** | H | **2d** |  | **3n** | 55 (4:1)[c] |
| 7 | **1b** | 4-Me | **2d** | | **3o** | 62 (5:2)[c] |
| 8 | **1c** | 3-Br | **2d** | | **3p** | 59 (3:1)[c] |
| 9 | **1d** | 4-$NO_2$ | **2d** | | **3q** | 35 (3:2)[c] |
| 10 | **1e** | 3-OMe | **2d** | | **3r** | 64 (6:1)[c] |

[a] Benzylidenemalononitrile **1** (10 mmol), C-H acid **2** (10 mmol), 20 mL of acetonitrile, undivided cell, 20 °C, 2.2 F $mol^{-1}$ , current density 50 mA $cm^{-2}$. [b] Isolated yield. [c] Ratio of izomers.

4-Methyl-7-oxo-2,6-diaryl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitriles **3m-3p** were obtained as mixtures of diastereomers. The structures of the major (2*RS*,3*SR*) **3m-3p** isomers were established earlier on the data of NOESY.[40] It should be noted that sodium bromide in methanol is a more effective mediator than PyHBr in acetonitrile for the electrochemical synthesis of spirocyclopropanes **3i-3p**.[29,40] Apparently this is due to the particularity of the reaction mechanism (Scheme 4).

A possible mechanism for the current transformation is proposed (Scheme 1). Bromine is formed at the anode and can be observed by its color. Deprotonation of the pyridinium cation at the cathode leads to the formation of pyridine. The evolution of hydrogen at the cathode is observed, especially when electrolysis is conducted without stirring of the reaction mixture. Deprotonation of the C-H acid by pyridine in solution and further bromination of the C-H acid anion forms the C-H acid **A**. Next, the ylide **B** is formed from the intermediate **A** by action of pyridine. Finally, addition of **B** to alkylidenemalononitrile gives rise to cyclopropane **3**. The last step was postulated by Abaszadeh in the chemical synthesis of cyclopropanes from pyridinium ylides and benzylidenemalononitriles.[41]




**Scheme 4**

## Conclusions

Summarizing, we have tested a novel mediator for electrochemical transformations. The electrochemical synthesis was performed under high constant current density in a simple undivided cell using a substoichiometric amount of pyridinium bromide as mediator. Utilization of pyridinium bromide allows to perform the electrolysis both in alcohols and aprotic solvents such as acetonitrile. After optimization of the reaction conditions, the tetracyanocyclopropanes, dimethyl 2,2-dicyano-3-arylcyclopropane-1,1-dicarboxylates and two types of spirocyclopropanes: 5,7-dimethyl-4,6,8-trioxo-2-aryl-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles and 4-methyl-7-oxo-2,6-diaryl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitriles have been synthesized. The reactions proceed in a simple undivided cell employing a substoichiometric amount of PyHBr that serves both as a mediator and a supporting electrolyte; in this manner additional conducting salt is not required. The developed technique allows the synthesis of gram-scale amounts of the target compounds.

## Experimental Section

**General.** All melting points were measured with a Gallenkamp melting point apparatus. $^1$H NMR and $^{13}$C NMR were recorded with a Bruker AM300 at ambient temperature in DMSO-$d_6$ or $CDCl_3$ solutions with working frequencies of 300.13 MHz and 75.47 MHz respectively. Chemical shifts values are given in δ scale 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 recorded with a Finningan MAT INCOS 50 spectrometer. High-resolution mass spectrometry (HRMS) (electrospray ionization, ESI) was measured on a BrukermicroTOF II instrument; external or internal calibration was done with an Electrospray Calibrant Solution (Fluka). Benzylidenemalononitriles **1** were synthesized by the condensation of the corresponding aromatic aldehydes and malononitrile *via* the Knoevenagel condensation.[15]

**General procedure.** An undivided cell was equipped with a graphite anode (area 5 cm$^2$) and Fe cathode (area 5 cm$^2$) and connected to a DC regulated power supply. To the cell were added the desired benzylidenemalononitrile **1** (10 mmol), C-H acid **2** (10 mmol), PyHBr (7.5 mmol), and 20 mL of acetonitrile. The mixture was electrolyzed (2.2 F mol$^{-1}$) using constant current conditions (50 mA/ cm$^2$) at 20 °C under magnetic stirring. When the reaction was completed, the solvent was removed under reduced pressure. The residue was poured into water, and the product was then extracted with dichloromethane (3 × 20 mL), dried over $Na_2SO_4$, and concentrated in vacuum. The residue was purified by crystallization from methanol to afford the desired cyclopropane **3**.

**3-Phenyl-1,1,2,2-tetracyanocyclopropane** (**3a**)**.** White solid; 1.57 g (72%); mp 226-228 °C (lit.[42] mp 229-230 °C). $^1$H NMR (DMSO-$d_6$): δ 5.10 (1H, s, CH), 7.48-7.80 (5H, m, Ar) ppm.

**3-(4-Methylphenyl)-1,1,2,2-tetracyanocyclopropane** (**3b**)**.** White solid; 1.53 g (66%); mp 224-227 °C (lit.[42] mp 226-229 °C). $^1$H NMR (DMSO-$d_6$): δ 2.31 (3H, s, $CH_3$), 5.20 (1H, s, CH), 7.28 (2H, d, *J* 8.0 Hz, Ar), 7.65 (2H, d, *J* 8.0 Hz, Ar) ppm.

**3-(3-Bromophenyl)-1,1,2,2-tetracyanocyclopropane** (**3c**)**.** White solid; 1.72 g (58%); mp 184-186 °C (lit.[42] mp 186-187 °C). $^1$H NMR (DMSO-$d_6$): δ 5.31 (1H, s, CH), 7.44 (1H, t, *J* 8.5 Hz, Ar), 7.68 (1H, d, *J* 8.5 Hz, Ar), 7.87(1H, d, *J* 8.5 Hz, Ar), 8.22 (1H, s, Ar) ppm.

**3-(4-Nitrophenyl)-1,1,2,2-tetracyanocyclopropane** (**3d**)**.** White solid; 1.26 g (48%); mp 232-234 °C (lit.[42] mp 232-234 °C). $^1$H NMR (DMSO-$d_6$): δ 5.52 (1H, s, CH), 8.20 (2H, d, *J* 8.8 Hz, Ar), 8.35 (2H, d, *J* 8.8 Hz, Ar) ppm.

**Dimethyl 2,2-dicyano-3-phenylcyclopropane-1,1-dicarboxylate (3e).** White solid; 1.90 g (67%); mp 124-126 °C. (lit.[12] mp 126-128 °C). $^1$H NMR (DMSO-$d_6$): δ 3.75 (s, 3H, $OCH_3$), 3.92 (s, 3H, $OCH_3$), 4.41 (s, 1H, CH), 7.35-7.50 (m, 5H, Ph) ppm.

**Dimethyl 2,2-dicyano-3-(4-methylphenyl)cyclopropane-1,1-dicarboxylate** (**3f**)**.** White solid; 1.87 g (63%); mp 134-13135 °C. (lit.[12] mp 137-139 °C). $^1$H NMR ($CDCl_3$): δ 2.39 (s, 3H, $CH_3$), 3.79 (s, 3H, $OCH_3$), 3.96 (s, 1H, CH), 3.98 (s, 3H, $OCH_3$), 7.18-7.30 (m, 4H, Ar) ppm.

**Dimethyl 2,2-dicyano-3-(3-bromophenyl)cyclopropane-1,1-dicarboxylate** (**3g**)**.** White solid; 2.32 g (64%); mp 110-111 °C (lit[12] mp 110-111 °C). $^1$H NMR ($CDCl_3$): δ 3.80 (s, 3H, $OCH_3$), 3.95 (s, 1H, CH), 3.97 (s, 3H, $OCH_3$), 7.26-7.35 (m, 2H, Ar), 7.50-7.55 (m, 2H, Ar) ppm.

**Dimethyl 2,2-dicyano-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate** (**3h**)**.** White solid; 1.25 g (38%); mp 141-143 °C. (lit.[12] mp 140-142 °C). $^1$H NMR ($CDCl_3$): δ 3.85 (s, 3H, $OCH_3$), 4.02 (s, 3H, $OCH_3$), 4.05 (s, 1H, CH), 7.62 (2H, d, *J* 8.0 Hz, Ar), 8.30 (2H, d, *J* 8.0 Hz, Ar) ppm.

**5,7-Dimethyl-4,6,8-trioxo-2-phenyl-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile** (**3i**)**.** White solid; 2.40 g (78%); mp. 258-260 °C (lit.[29] mp 259-260 °C). $^1$H NMR (DMSO-*d*$_6$): δ 3.12 (s, 3H, $CH_3$), 3.27 (s, 3H, $CH_3$), 4.36 (s, 1H, CH), 7.32-7.40 (m, 3H, Ar), 7.44-7.50 (m, 2H, Ar) ppm.

**5,7-Dimethyl-2-(4-methylphenyl)-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile** (**3j**)**.** White solid; 2.09 g (65%); mp. 203-204 °C (lit.[29] mp 203-204 °C). $^1$H NMR (DMSO-*d*$_6$): δ 2.30 (s, 3H, $CH_3$), 3.12 (s, 3H, $CH_3$), 3.26 (s, 3H, $CH_3$), 4.29 (s, 1H, CH), 7.17 (d, *J* 7.9 Hz, 2H, Ar), 7.33 (d, *J* 7.9 Hz, 2H, Ar) ppm.

**2-(3-Bromophenyl)-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile** (**3k**)**.** White solid; 2.86 g (74%); mp. 222-224 °C (lit.[29] 220-222 °C). $^1$H NMR (DMSO-*d*$_6$): δ 3.12 (s, 3H, $CH_3$), 3.28 (s, 3H, $CH_3$), 4.39 (s, 1H, CH), 7.35 (t, *J* 7.9 Hz, 1H, Ph), 7.50-7.57 (m, 2H, Ph), 7.77-7.79 (m, 1H, Ph) ppm.

**5,7-Dimethyl-2-(4-nitrophenyl)-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile** (**3l**)**.** Yellowish solid; 1.90 g (54%); mp. 219-221 °C (lit.[29] 219-221 °C). $^1$H NMR (DMSO-*d*$_6$): δ 3.12 (s, 3H, $CH_3$), 3.30 (s, 3H, $CH_3$), 4.55 (s, 1H, CH), 7.82 (d, *J* 8.4 Hz, 2H, Ar), 8.24 (d, *J* 8.4 Hz, 2H, Ar).

**5,7-Dimethyl-2-(3-methoxyphenyl)-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile** (**3m**)**.** White solid; 2.23 g (66%); mp. 232-234 °C. $^1$H NMR (DMSO-*d*$_6$): δ 3.12 (s, 3H, $CH_3$), 3.26 (s, 3H, $CH_3$), 4.08 (s, 1H, CH), 3.76 (s, 3H, $OCH_3$), 6.90-7.12 (m, 2H, Ar), 7.20-7.44 (m, 2H, Ar) ppm; $^{13}$C NMR (DMSO-*d*$_6$): δ 23.4, 28.4, 29.1, 40.1, 41.2, 55.5, 109.4, 110.9, 112.4, 115.9, 120.7, 128.2, 130.6, 150.3, 157.0, 160.6, 163.0 ppm. IR (KBr): 768, 1396, 1424, 1440, 1684, 1708, 2248 cm$^{-1}$. HRMS (ESI) 339.1093 $[M+H]^+$, calcd for $C_{17}H_{15}N_4O_4$: 339.1099.

**4-Methyl-7-oxo-2,6-diphenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile** (**3n**)**.** White solid; 1.79 g (55%); diastereomeric ratio 4:1; mp 187-189 °C (lit.[43] mp 187-189 °C). $^1$H NMR (DMSO-*d*$_6$) major diastereoisomer: δ 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) ppm; minor diastereoisomer: δ 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) ppm.

**4-Methyl-2-(4-methylphenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile** (**3o**)**.** White solid; 2.10 g (62%); diastereomeric ratio 5:2; mp 168-170 °C (lit.[43] mp 175-178 °C). $^1$H NMR (DMSO-*d*$_6$) major diastereoisomer: δ 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) ppm; minor diastereoisomer: δ 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) ppm.

**2-(3-Bromophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile** (**3p**)**.** White solid; 2.39 g (59%); diastereomeric ratio 3:1; mp 194-196 °C (lit.[43] mp 198-200 °C). $^1$H NMR (DMSO-*d*$_6$) major diastereoisomer: δ 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) ppm; minor diastereoisomer: δ 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) ppm.

**4-Methyl-2-(4-nitrophenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile** (**3q**)**.** White solid; 1.30 g (38%); diastereomeric ratio 3:2; mp 169-172 °C (lit.[43] mp 161-163 °C). $^1$H NMR (DMSO-*d*$_6$) major diastereoisomer: δ 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) ppm; minor diastereoisomer: δ 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) ppm.

**4-Methyl-2-(3-methoxyphenyl)-7-oxo-6-phenyl-5,6-diazaspiro[2.4]hept-4-ene-1,1-dicarbonitrile** (**3r**)**.** White solid; 2.28 g (64%); diastereomeric ratio 6:1; mp 188-190 °C. $^1$H NMR (DMSO-*d*$_6$) major diastereoisomer: δ 1.78 (s, 3H, $CH_3$), 3.78 (s, 3H, $OCH_3$), 4.02 (s, 1H, CH), 7.20-7.32 (5H, m, Ar), 7.34-7.52 (2H, m, Ar), 7.88-7.96 (2H, m, Ar) ppm; $^{13}$C NMR (DMSO-*d*$_6$): δ 16.6, 20.4, 40.7, 44.9, 55.5, 111.1, 111.7, 114.8, 118.5 (2C), 119.8, 123.7, 129.3 (2C), 129.6, 130.9, 132.6, 133.4, 150.8, 159.8, 165.1. IR (KBr): 768, 1248, 1424, 1480, 1608, 1708, 2254 cm$^{-1}$. HRMS (ESI) 357.1360 $[M+H]^+$, calcd for $C_{21}H_{17}N_4O_2$: 357.1352.

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