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The first example of the cascade assembly of a spirocyclopropane structure: direct transformation of benzylidenemalononitriles and *N,N′*-dialkylbarbituric acids into substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles

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ABSTRACT

The direct formation of substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles in 75–95% yields from benzylidenemalononitriles and *N,N′*-dialkylbarbituric acids is described.

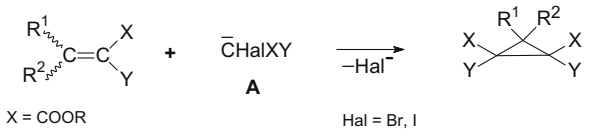
The discovery of new synthetic methodologies to facilitate the preparation of organic compounds is a pivotal focal point of research activity in the field of modern organic, bioorganic and medicinal chemistry.[1] The cyclopropyl group is a vital structural unit in many synthetic and naturally occurring compounds, exhibiting a wide spectrum of biological properties ranging from enzyme inhibition to herbicidal, antibiotic, antitumor and antiviral activities.[2–4] Thus, the prevalence of cyclopropane-containing compounds possessing biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis.

On the other hand, barbiturates (derivatives of barbituric acid) are a class of drugs that act as central nervous system depressants, and by virtue of this, they produce a wide spectrum of effects, from mild sedation to anaesthesia and are also effective as anxiolytics and as anticonvulsants. They have additional pharmacological potential as analeptics, immunomodulating and anti-AIDS agents, and also as anticancer remedies.[5] Spirobarbiturates are a class of compounds with interesting pharmacological and physiological activity.[6]

Thus, the 5,7-diazaspiro[2.5]octane system appears to be of the interest because it incorporates spiro-connected cyclopropane and hexahydropyrimidine-2,4,6-trione heterocyclic ring which in combination may be promising with respect to biological responses.

Although methods for cyclopropane synthesis are numerous, they can be classified into two main groups: (1) intramolecular cyclization, and (2) interaction of two different molecules (addition of carbenes to olefins or Michael initiated ring closure (MIRC) are the best known examples of this type).[2,4] MIRC plays an important role in organic chemistry and many synthetic examples are described in the literature.[7]

The well-known MIRC to substituted cyclopropanes involves the addition of halogeno-substituted CH-acid anions (**A**), generated by the action of a base on the corresponding CH-acid (**AH**), to conjugated activated olefins followed by cyclization with elimination of the halide anion[8] (Scheme 1).



Scheme 1.

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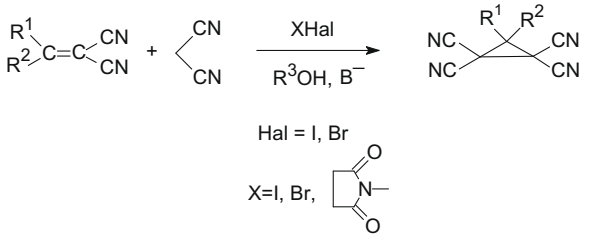


Scheme 2.

Cascade reactions have been utilized as powerful methods to construct molecular complexity from readily available starting materials by combining two or more reactions into a single transformation.[9] As such, cascade reactions are of increasing importance in modern organic chemistry. This is not only due to the need for more efficient and less labour-intense methodologies for the synthesis of organic compounds, but also the consequence of the increasing importance of environmental considerations in chemistry.

Recently, we reported a new strategy to cyclopropanes: the direct cascade transformation of benzylidenemalononitriles and malononitrile into 1,1,2,2-tetracyanocyclopropanes (Scheme 2).[10] In this reaction halogenation of the CH-acid was followed by a Michael addition step, thus an abbreviation for this type of cyclopropane formation reaction should be MHIRC—Michael Halogenation Initiated Ring Closure reaction.

In the present study, we report our results on the direct 'one-pot' cascade transformation of benzylidenemalononitriles and *N,N′*-dialkylbarbituric acids into 2-aryl-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles (Scheme 3, Tables 1 and 2), which is to our knowledge, the first example of the cascade assembly of the spirocyclopropane structure.

First, to evaluate the synthetic potential of the proposed procedure and to optimize the conditions, the transformation of benzylidenemalononitrile **1a** and *N,N′*-dimethylbarbituric acid **2a** into 5,7-dimethyl-4,6,8-trioxo-2-phenyl-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile **3a** was studied (Table 1).

Excellent conversions of the starting compounds and a 95% yield of 5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile **3a** were obtained when the reaction was carried out in ethanol in the presence of 1.2 equivalents of EtONa and bromine (Table 1, entry 3). Increasing quantity of EtONa led to a decrease of the reaction yield, which may result from undesired base-induced oligomerization of the starting benzylidenemalononitile.[12]

Under the optimal conditions, that is, bromine as the active halogen compound, 1.2 equiv of EtONa as base, and ethanol as solvent, substituted benzylidenemalononitriles **1a**–**i** and *N,N′*-dialkylbarbituric acids **2a**,**b** were transformed into the corresponding substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles **3a**–**k** in 75–95% yields (Table 2).

Table 1
Influence of EtONa amount on the yield of **3a**[a,11]

Entry	EtONa (equiv)	Yield of **3a**[b] (%)
1	0.5	59
2	1.0	71
3	1.2	95
4	1.5	83
5	2.0	67

[a] 10 mmol of **1a**, 10 mmol of **2a**, 20 ml of EtOH, 0.5–2.0 mmol of EtONa, 10 mmol of bromine, 3 h.
[b] Isolated yield.

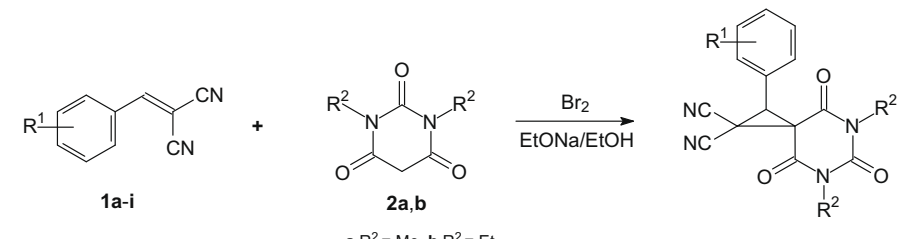
Table 2
Direct transformation of substituted benzylidenemalononitriles **1a**–**i** and *N,N′*-dialkylbarbituric acids **2a**,**b** into substituted 2-aryl-4,6,8-trioxo-5,7-diaza-spiro[2.5]octane-1,1-dicarbonitriles **3a**–**k**[a,11]

R^1	Benzylidene-malononitrile	R^2	Barbituricacid	Product, yield[b] (%)
H	**1a**	Me	**2a**	**3a**, 95
4-Me	**1b**	Me	**2a**	**3b**, 93
2-MeO	**1c**	Me	**2a**	**3c**, 81
4-*t*-Bu	**1d**	Me	**2a**	**3d**, 80
2-Cl	**1e**	Me	**2a**	**3e**, 85
3-Cl	**1f**	Me	**2a**	**3f**, 83
3-Br	**1g**	Me	**2a**	**3g**, 87
4-NO_2	**1h**	Me	**2a**	**3h**, 95
H	**1a**	Et	**2b**	**3i**, 75
4-Me	**1b**	Et	**2b**	**3j**, 77
4-Cl	**1i**	Et	**2b**	**3k**, 81

[a] 10 mmol of benzylidenemalononitrile, 10 mmol of barbituric acid, 20 ml of EtOH, 12 mmol of EtONa, 10 mmol of bromine, 3 h.
[b] Isolated yield.

Taking into consideration the data obtained and our previous results on the transformation of benzylidenemalononitriles and malononitrile into substituted tetracyanocyclopropanes,[10] the following mechanism is proposed (Scheme 4).

The first step involves Michael addition of *N,N′*-dimethylbarbituric acids **2a**,**b** to the benzylidenemalononitriles **1a**–**i** in the presence of the base to give anion **B**. Next, bromination of anion **B** leads to substituted 2-aryl-1-bromo-2-(1,3-dialkyl-2,4,6-trioxohexahydropyrimidin-5-yl)ethane-1,1-dicarbonitrile **4**. Cyclization of **4** to substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile **3** takes place in accordance with the earlier reported data (Scheme 4).[10,13] It should be mentioned that the final step of the mechanism (Scheme 4) is similar to that for the



1a-i

a R^1 = H, **b** R^1 = 4-Me, **c** R^1 = 2-MeO, **d** R^1 = 4-*t*-Bu, **e** R^1 = 2-Cl, **f** R^1 = 3-Cl, **g** R^1 = 3-Br, **h** R^1 = 4-NO_2, **i** R^1 = 4-Cl

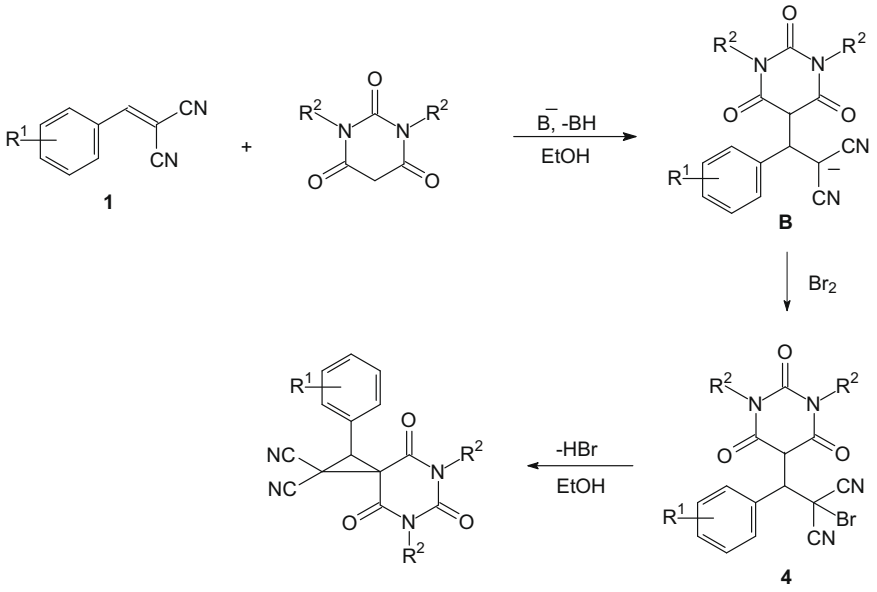
2a,**b**

a R^2 = Me, **b** R^2 = Et

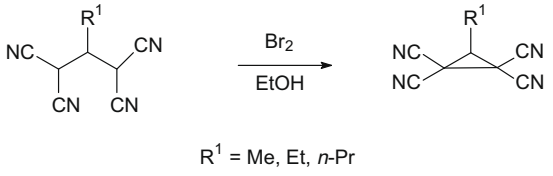
3a-k

a R^1 = H, R^2 = Me; **b** R^1 = 4-Me, R^2 = Me; **c** R^1 = 2-MeO, R^2 = Me; **d** R^1 = 4-*t*-Bu, R^2 = Me; **e** R^1 = 2-Cl, R^2 = Me; **f** R^1 = 3-Cl, R^2 = Me; **g** R^1 = 3-Br, R^2 = Me; **h** R^1 = 4-NO_2, R^2 = Me; **i** R^1 = H, R^2 = Et; **j** R^1 = 4-Me, R^2 = Et; **k** R^1 = 4-Cl, R^2 = Et

Scheme 3.



Scheme 4.



Scheme 5.

synthesis of 3-substituted tetracyanocyclopropanes as reported by Mariella and Roth.[13] This method includes bromination of 2-alkyl-substituted 1,1,3,3-tetracyanopropanes in ethanol followed by cyclization and formation of 3-alkyl substituted 1,1,2,2-tetracyano-substituted cyclopropanes (Scheme 5).[13]

Thus, a new type of cascade 'one-pot' reaction for the direct formation of spirocyclopropanes from benzylidenemalononitriles and *N*,*N*′-dialkylbarbituric acids has been reported. The action of bromine on equimolar amounts of benzylidenemalononitrile and *N*,*N*′-dialkylbarbituric acid in basic ethanol solution results in the formation of substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles in 75–95% yields.

The procedure utilises inexpensive reagents, is easily carried out and the work up is not complicated. 2-Aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles crystallized directly from the reaction mixture, and consequently, the products were isolated by the filtration and washing with warm water.

The 5,7-diazaspiro[2.5]octane system appears to be of interest because it incorporates a cyclopropane unit and a hexahydropyrimidine-2,4,6-trione heterocyclic ring which are promising with respect to biological responses.

Acknowledgements

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11. *General procedure.* To a 10 mL ethanol solution of benzylidenemalononitrile **1** (10 mmol) and barbituric acid **2** (10 mmol) in a 50 ml beaker, 0.82 g (12 mmol) of sodium ethoxide in 10 mL of ethanol was added over 1 min. Then 10 mmol

(0.51 mL) of bromine was added over 1 min without external cooling. The mixture was magnetically stirred at room temperature for 3 h. After which the solid phase was filtered, washed with warm water and dried in a desiccator over P_2O_5 to afford pure **3**. *5,7-Dimethyl-4,6,8-trioxo-2-phenyl-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile* **3a**, mp 259–260 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.44–7.50 (m, 2H), 7.32–7.40 (m, 3H), 4.36 (s, 1H), 3.28 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.93, 160.50, 150.88, 129.20, 128.61, 128.21, 128.16, 112.37, 110.82, 43.88, 41.29, 29.02, 28.55, 23.50; MS (EI, 70 eV): *m/z* (%) 308 (23) [M$^+$], 281 (16), 251 (45), 194 (88), 166 (100), 139 (66); IR (KBr, cm^{-1}) 2252, 1704, 1456, 1444, 1424, 1392, 1300, 752; Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.21; H, 4.05; N, 18.03.*2-(2-Methoxyphenyl)-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile* **3c**, mp 229–230 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36–7.42 (m, 2H), 6.96–7.08 (m, 2H), 4.01 (s, 1H), 3.73 (s, 3H), 3.30 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.12, 160.48, 156.80, 150.70, 130.26, 130.07, 120.28, 116.11, 112.41, 110.98, 110.86, 55.59, 41.01, 40.79, 29.07, 28.54, 23.63; MS (EI, 70 eV): *m/z* (%) 338 (26) [M$^+$], 307 (70), 273 (34), 243 (16), 224 (56), 181 (100); IR (KBr, cm^{-1}) 2252, 1704, 1684, 1460, 1444, 1424, 1388, 768; Anal. Calcd for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.23; H, 4.31; N, 16.48.*2-(3-Bromophenyl)-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile* **3g** mp 217–219 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.77–7.79 (m, 1H), 7.50–7.57 (m, 2H), 7.35 (t, 1H, *J* = 7.9 Hz), 4.39 (s, 1H), 3.28 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.70, 160.58, 150.89, 132.05, 131.35, 131.09, 130.23, 128.28, 121.17, 112.12, 110.64, 42.44, 41.24, 29.01, 28.56, 23.60; MS (EI, 70 eV): *m/z* (%) 388 (11) [^{81}Br, M$^+$], 386 (11) [^{79}Br, M$^+$], 361 (8), 359 (8), 331 (8), 329 (8), 307 (28), 274 (21), 272 (20), 193 (100); IR (KBr, cm^{-1}) 2252, 1708, 1680, 1460, 1424, 1388, 1300, 752; Anal. Calcd for $C_{16}H_{11}BrN_4O_3$: C, 49.63; H, 2.86; Br, 20.64; N, 14.47. Found: C, 49.47; H, 3.01; Br, 20.59; N, 14.29.*5,7-Diethyl-4,6,8-trioxo-2-phenyl-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile* **3i**, mp 186–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36–7.46 (m, 3H), 7.22–7.32 (m, 2H), 4.29 (s, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.95 (dq, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.49, 160.13, 149.91, 129.09, 128.67, 128.19, 128.07, 112.41, 110.86, 43.84, 41.41, 38.67, 37.55, 23.47, 12.63, 12.53; MS (EI, 70 eV): *m/z* (%); 237 (6, M$^+$–O=C–N(Et)–C=O), 194 (96), 166 (100), 139 (58), 70 (78), 56 (62); IR (KBr, cm^{-1}) 2252, 1704, 1684, 1456, 1444, 1408, 1380, 1316; Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.20; H, 4.88; N, 16.52.

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