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Selective and efficient electrocatalytic way to spirobarbituric dihydrofurans

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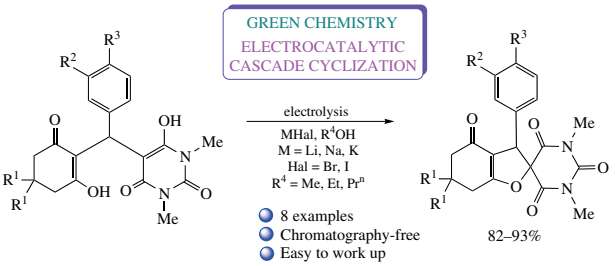
Electrocatalytic cyclization of 6-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(aryl)methyl]-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-diones in alcohols in an undivided cell in the presence of sodium halides results in selective formation of substituted spirobarbituric dihydrofurans in 82–93% yields. Crystal structure of 3-(3-bromophenyl)-1′,3′,6,6-tetramethyl-3,5,6,7-tetrahydro-2′,4-dihydrospiro[benzofuran-2,5′-pyrimidine]-2′,4,4′,6′(1′*H*,3′*H*)-tetraone has been confirmed by X-ray diffraction data.



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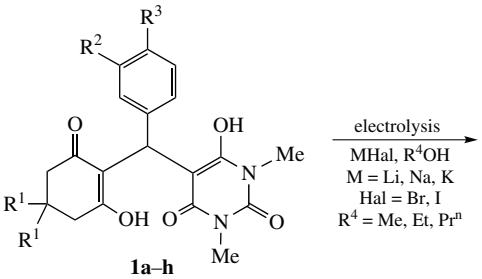
Electrochemical synthesis of organic compounds has become a useful method with important synthetic and ecological advantages.[1] Nevertheless, the employment of classical electrochemical procedures is hampered by complex equipment and long reaction time. Thus, electrocatalytic oxidation in the presence of mediatory systems becomes a promising approach.[2] These systems allow one to make use of undivided cells, which considerably simplify the electrolysis. The redox pair halide anion–halogen represents one of the most suitable mediators for selective organic synthesis.[3] Electrolysis in an undivided cell in alcohol as a solvent in the presence of alkali metal halides results in generation of alkoxide anion at the cathode and halogen at the anode, then these moieties activate a cascade oxidative cycle in solution, with halide anion and the alcohol returning to the electrodes upon completion of the cycle. The mild catalytic nature of the mediatory oxidative process enables employment of low concentrations of base and halogen along with a neutral pH, which seem to be key factors for the reaction selectivity and high product yield.

Heterocycles are important structural components in medicinal chemistry[4] found in many biologically significant molecules such as enzymes, vitamins and other natural products as well as various pharmaceuticals with antifungal, anti-inflammatory, antimicrobial, antioxidant, anticonvulsant, antiallergic, anti-HIV and anticancer activity.[5] Among the nitrogen containing heterocycles, barbiturates (pyrimidine-2,4,6-triones) attract attention in medicinal chemistry due to their effects on the central nervous system.[6] Current focus on barbiturates arises also from their potential as anti-AIDS, anticancer and antioxidant agents.[7–10]

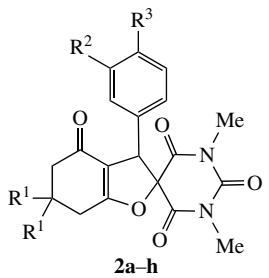
Spiro compounds have a good balance of conformational rigidity and flexibility to fit different molecular targets and thus increase the chance of finding bioactive hits.[11,12] In particular, spirobarbiturates deserve attention due to their unique structural assembly and the associated range of pharmaceutical properties.[13] Thus, they exhibit anticonvulsant and sedative effects[14] as well as inhibit matrix metalloproteinase-13 (MMP-13)[15] and dihydroorotate dehydrogenase (DHODase).[16] As a further example, preparation has been described for 1-(4-phenoxyphenyl)-5,7-diazaspiro[2.5]octane-4,6,8-trione as a potential inhibitor of tumor necrosis factor-α (TNF-α) for the treatment of various inflammatory, infectious, immunological and malignant diseases.[17]

Considering our experience in the electrocatalytic cascade and multicomponent reactions resulting in spiro compounds[18] as well as the known biomedical applications of spirobarbiturates, in this work we designed a convenient electrocatalytic cascade methodology for selective and efficient cyclization of recently obtained 6-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)-(aryl)methyl]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **1a–h**[19] into spirobarbituric dihydrofurans **2a–h**. The cyclization was carried out in alcohols in an undivided cell in the presence of alkali metal halides (Scheme 1 and Table 1).

In the first step we optimized conditions for the transformation of compound **1a** into spiro derivative **2a** (Table 1). NaBr was



1a–h



2a–h

a $R^1 = R^2 = R^3 = H$, 87%
b $R^1 = R^2 = H$, $R^3 = OMe$, 84%
c $R^1 = R^2 = H$, $R^3 = F$, 86%
d $R^1 = R^3 = H$, $R^2 = Cl$, 83%
e $R^1 = Me$, $R^2 = R^3 = H$, 82%
f $R^1 = R^2 = Me$, $R^3 = H$, 85%
g $R^1 = Me$, $R^2 = H$, $R^3 = Cl$, 90%
h $R^1 = Me$, $R^2 = Br$, $R^3 = H$, 93%

Scheme 1

Table 1 Electrocatalytic cyclization of compound **1a** into spirobarbituric dihydrofuran **2a**.[a]

Entry	Solvent	Mediator	*t*/min	Electricity passed/F mol^{-1}	Isolated yield of **2a** (%)
1	MeOH	NaBr	32	2.0	79
2	MeOH	KBr	32	2.0	75
3	MeOH	LiBr	32	2.0	72
4	MeOH	NaI	32	2.0	65
5	EtOH	NaBr	32	2.0	74
6	*n*-PrOH	NaBr	32	2.0	71
7	MeOH	NaBr	35	2.2	87
8	MeOH	NaBr	40	2.5	83

[a] Solution of compound **1a** (5 mmol) and NaBr (3 mmol) in alcohol (20 ml); iron cathode (5 cm^2), graphite anode (5 cm^2), undivided cell, reaction performed at 20 °C at current density 100 mA cm^{-2}.

found to be the most efficient mediator among the other alkali metal halides tested. In the row of alcohols as the solvents, methanol was estimated as the most suitable one. Slight excess of the electricity passed through the cell, namely 2.2 F mol^{-1}, resulted in the best yield of spiro product **2a** (87%, Table 1, entry 7).

Under the optimized conditions, compounds **1a–h** were selectively cyclized into the corresponding spirobarbituric dihydrofurans **2a–h** in 82–93% yields.† The structure of new compounds **2a–h** was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy as well as mass spectrometry and elemental analysis data (for details, see Online Supplementary Materials). For all the products only one set of signals was observed in ^{1}H and ^{13}C NMR spectra. The structure of compound **2h** was additionally verified using X-ray diffraction (Figure 1 and Online Supplementary Materials).‡

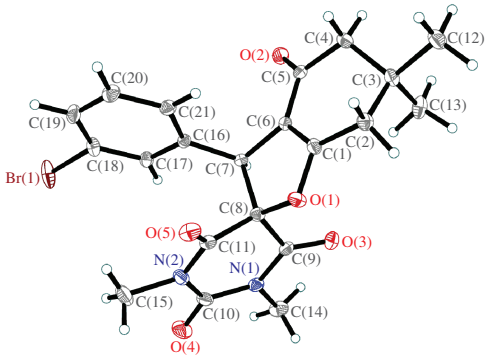
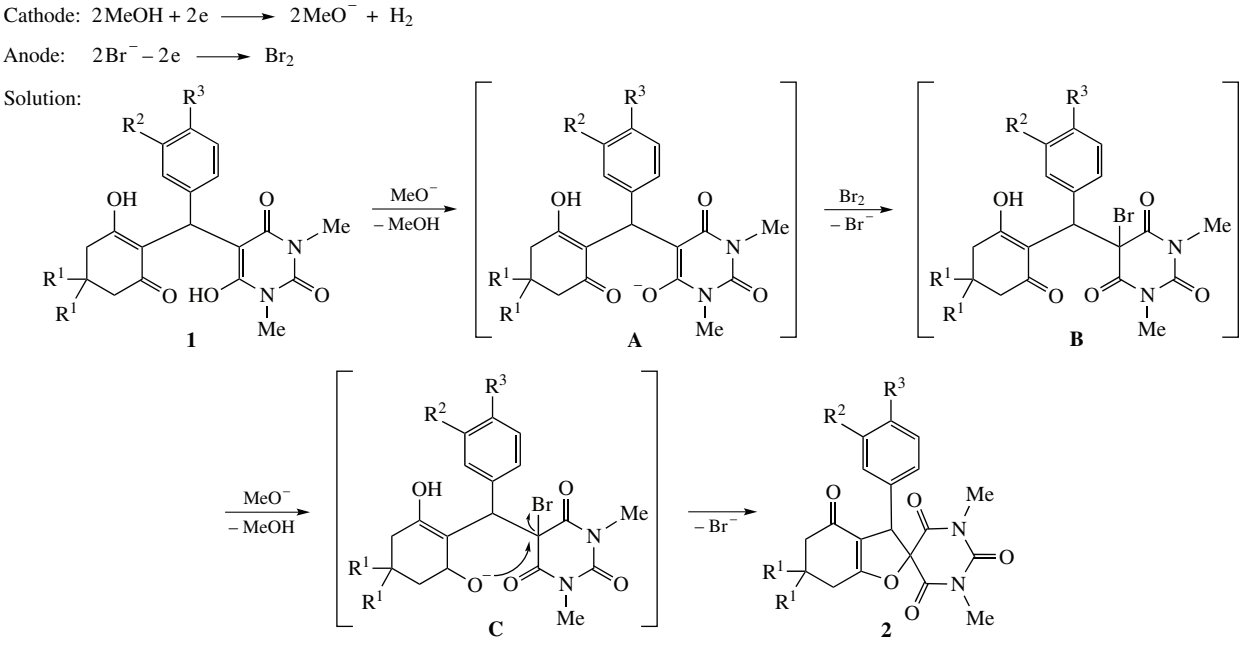


Figure 1 Molecular structure of compound **2h** with thermal ellipsoids at 50% probability level.

Taking into consideration the synthetic results and the known data on electrocatalytic reactions mediated by bromides,[20] a mechanism for the cyclization of compounds **1a–h** into spirobarbituric dihydrofurans **2a–h** was proposed (Scheme 2).

The cathodic process consists in evolution of hydrogen accompanied by the generation of methoxide anion. The anodic process comprises the formation of bromine. In the absence of stirring, the corresponding brown color was observed near the anode. Reaction in solution between methoxide ion and compound **1** resulted in formation of anion **A**. Then bromination leads to compound **B**, which by the action of one more methoxide anion cyclizes into spirobarbiturate **2** through enolate **C**, with regeneration of bromide ion.

In conclusion, the electrocatalytic cyclization developed represents a facile and efficient way to new substituted spirobarbituric dihydrofurans with both babituric acid and 3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one moieties. The procedure employs simple equipment, an undivided cell,



Scheme 2

† *General procedure for the preparation of compounds* **2a–h**. A solution of compound **1** (5 mmol) and sodium bromide (0.3 g, 3 mmol) in methanol (20 ml) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 20 ºC under a constant current density of 100 mA cm^{-2} (I = 500 mA at electrodes area 5 cm^2) until 2.2 F mol^{-1} of electricity had been passed. Then the reaction mixture was concentrated to 4 ml volume and cooled to 0 °C, the crystallized solid product was filtered out, rinsed twice with an ice-cold ethanol–water solution (1 : 1, 4 ml) and dried *in vacuo*.

‡ *Crystal data for* **2h**. $C_{21}H_{21}BrN_2O_5$, 461.31 g mol^{-1}, orthorhombic, space group $Pna2_1$ at 100(2) K, a = 19.5349(8), b = 18.2072(7) and c = 5.5716(2) Å, V = 1981.68(13) Å^3, Z = 4, d_{calc} = 1.546 g cm^{-3}, μ(MoKα) = 2.111 mm^{-1}, 72362 reflections measured (2.09° ⩽ 2θ ⩽ 34.65°), 8361 unique reflections (R_{int} = 0.0618), which were used in all the calculations. The final R_1 was 0.0366 [$I > 2\sigma(I)$] and wR_2 was 0.0715.

CCDC 2049440 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

available and cheap sodium bromide as mediator as well as uncomplicated isolation procedure. The approach used is suitable for environmentally benign diversity-oriented large-scale processes, for example the synthesis of new drug libraries. The products represent promising pharmacology active heterocyclic systems for potential biomedical applications like anticonvulsant, anti-AIDS and anti-inflammatory remedies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.021.

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