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A fast and efficient 'on-solvent' cascade assembling of salicylaldehydes and dimethylbarbituric acid into 5-(1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones

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Abstract: A fast (15 min) and efficient cascade reaction of salicylaldehydes and 1,3-dimethylbarbituric acid in the presence of *p*-TsOH as a catalyst furnishes substituted 5-(1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **1a–h**, containing both chromeno[2,3-*d*]pyrimidine and hexahydropyrimidine-2,4,6-trione pharmacologically active fragments, in 95–99% yields. This new procedure is characterized by the use of inexpensive reagents and a simple workup.

Keywords: barbiturates; cascade reaction; catalysis; chromeno[2,3-*d*]pyrimidines; cyclization; salicylaldehydes.

Introduction

Cascade reactions are an important way to produce complex organic compounds from simple and readily available components in a 'one-pot' procedure in which two or more successive reactions are carried out as a single transformation [1, 2]. Cascade reactions are especially useful in the synthesis of polycyclic and spiro compounds using modern 'green chemistry' [3]. Thus, the demand for efficient and less labor-intensive methods and the environmental factors are fuelling progress in the cascade reaction strategy [4, 5].

Recently, 'on-water' [6–8] and 'on-solvent' [9–11] methodologies have been suggested to carry out cascade and multicomponent reactions in water or solvent using reagent mixtures and emulsions in the absence of full solubility of components to increase the selectivity and the efficiency of the desired complex synthetic processes. In particular, the concept of 'privileged medicinal structures or scaffolds', is one of the main ideas of drug discovery in last decades [12].

Barbituric acids (hexahydropyrimidine-2,4,6-triones) are known as a privileged medicinal scaffold, transformations of which lead to important 5-substituted derivatives, the so-called barbiturates. Barbiturates are often used as pharmaceuticals with a wide spectrum of anesthetic and anticonvulsant effects [13, 14]. In recent years, barbiturates have been used in clinical practice as analeptic, anti-AIDS and anticancer agents [15–17].

Chromeno[2,3-*d*]pyrimidines contain both pharmacologically important chromene and pyrimidine moieties. For this class of compounds, a large spectrum of pharmacological properties is known including antitumor, cytotoxic [18], antioxidant [19], antiplatelet, antithrombotic [20] and anti-inflammatory activities [21]. Moreover, chromeno[2,3-*d*]pyrimidines show interesting photophysical properties [22]. Compounds **1** described in this report combine in one molecule hexahydropyrimidine-2,4,6-trione and chromeno[2,3-*d*]pyrimidine systems, which are part of many biologically active agents.

Few methods are known for the cascade synthesis of chromeno[2,3-*d*]pyrimidin-5-yl-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **1** (Scheme 1) from salicylaldehydes and barbituric acids. Both bases and acids are known as catalysts for this cascade process. In the presence of piperidine, the reaction of salicylaldehyde with two equivalents of *N*,*N*′-dimethylbarbituric acid in boiling ethanol for 5 h furnished compound **1a** in a 43% yield [23]. Hydrochloric acid was used as a catalyst in the reaction of salicylaldehyde or 5-bromosalicylaldehyde with *N*,*N*′-dimethylbarbituric acid in boiling methanol [24]. A limited, non-catalytic reaction in boiling ethanol has also been described [25]. Recently, an unusual variant of the synthesis of compounds **1** has been suggested by the cascade reaction of a salicylaldehyde and two equivalents of 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione in the presence of 1,1′-sulfinyldipyridinium bis(hydrogen sulfate) in boiling ethanol for 5–10 h [26]. These methods for the synthesis of compounds **1** have limitations including a low yield, a long reaction time or the requirement of using a non-common catalyst. The successful approach

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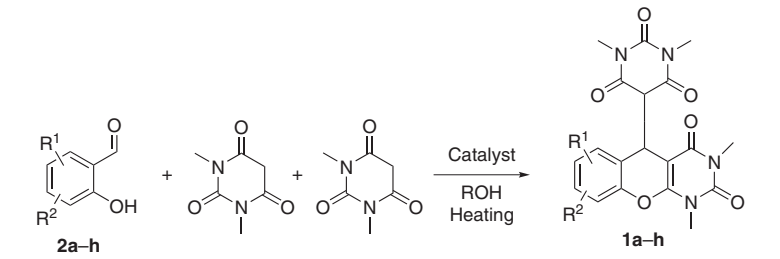


a: R^1 = H; R^2 = H
b: R^1 = H; R^2 = 4-Me
c: R^1 = H; R^2 = 3-MeO
d: R^1 = H; R^3 = 5-Cl
e: R^1 = H; R^2 = 5-Br
f: R^1 = H; R^2 = 5-NO_2
g: R^1 = 3-OMe; R^2 = 5-Br
h: R^1 = 3-Cl; R^2 = 5-Cl

a: R^1 = H; R^2 = H
b: R^1 = H; R^2 = 8-Me
c: R^1 = H; R^2 = 9-MeO
d: R^1 = H; R^2 = 7-Cl
e: R^1 = H; R^2 = 7-Br
f: R^1 = H; R^2 = 7-NO_2
g: R^1 = 9-OMe; R^2 = 7-Br
h: R^1 = 9-Cl; R^2 = 7-Cl

Scheme 1 Cascade assembling of salicylaldehydes **2a–h** and *N*,*N*′-dimethylbarbiturate into products **1**.

to compounds **1**, described in this report, is part of our ongoing research on multicomponent and cascade transformation of C-H acids and carbonyl compounds [27–31].

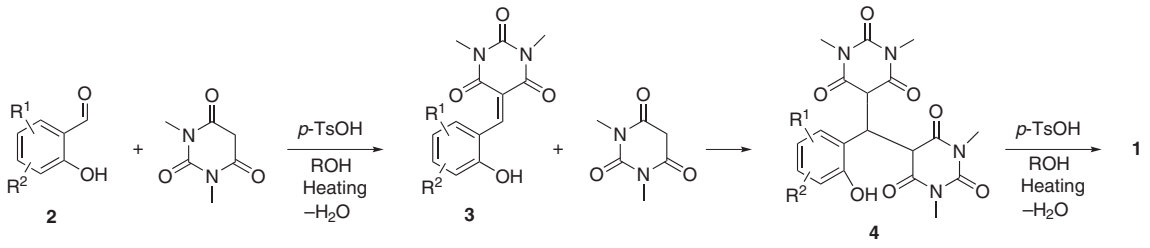
Results and discussion

This report describes a 'one-pot' cascade reaction of a salicylaldehyde **2** and two equivalents of *N*,*N*′-dimethylbarbiturate leading to a chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **1** (Scheme 1). Initially, the cascade transformation of salicylaldehyde **2a** and *N*,*N*′-dimethylbarbiturate into chromeno[2,3-*d*]pyrimidine **1a** was studied using alcohol emulsions. In a typical experiment, the mixture of salicylaldehyde **2a** (3 mmol, 0.37 g) and *N*,*N*′-dimethylbarbiturate (6 mmol, 0.94 g) and 3 mL of alcohol was magnetically stirred. In boiling ethanol (78°C) the chromeno[2,3-*d*] pyrimidine **1a** was formed in a 33% yield in 15 min.

The same reaction in boiling *n*-propanol (97°C) afforded product **1a** in a 40% yield. In *n*-propanol, with NaOAc or KF as a catalyst (10 mol%) product **1a** was obtained in a 45% and 48% yield, respectively. The use of $LiClO_4$, iodine or HCl as a catalyst resulted in the respective yield of **1a** of 53%, 65% and 71%. The yield of **1a** increased to 99% for the reaction conducted in *n*-propanol for 15 min under reflux in the presence of *p*-TsOH (10 mol%). Decreasing the reaction time to 10 min under otherwise similar conditions resulted in the formation of **1a** in a 90% yield. Overall, under optimized conditions, stirring the emulsion of salicylaldehyde **2a–h**, N,*N*′-dimethylbarbiturate and a catalytic amount of *p*-TsOH in boiling *n*-propanol for 15 min furnished chromeno[2,3-*d*]pyrimidine **2a–h** in a 95–99% yield.

On the basis of these results and the mechanistic data on cascade reactions of carbonyl compounds with barbituric acids published previously [32–34], the following mechanism for the cascade reaction of a salicylaldehyde and *N*,*N*′-dimethylbarbiturate can be suggested (Scheme 2).

First, the Knoevenagel condensation of salicylaldehyde **2** with *N*,*N*′-dimethylbarbiturate generates the intermediate product **3**. In the second step, the Michael addition of the second molecule of *N*,*N*′-dimethylbarbiturate to the electron deficient compound **3** results in the formation of the adduct **4**. Finally, cyclization of the Michael adduct **4** leads to the observed chromeno[2,3-*d*]pyrimidine **1**.



Scheme 2 Suggested mechanism for the formation of products **1**.

Conclusion

A fast (15 min) and highly efficient direct reaction of substituted salicylaldehydes and *N*,*N*′-dimethylbarbiturate in boiling *n*-propanol in the presence *p*-TsOH as a catalyst into substituted compounds **1** is described. Upon cooling, analytically pure products **1** precipitate directly from the mixture.

Experimental

All melting points were measured with a Gallenkamp melting-point apparatus and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75 MHz) nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 using a Bruker Avance II 300 spectrometer at ambient temperature. Infrared (IR) spectra were recorded with a Bruker ALPHA-T Fourier-transform infrared (FT-IR) spectrometer in KBr pellets. Electron ionization (EI) mass spectra were obtained at 70 eV on a Kratos MS-30 spectrometer equipped with a direct inlet system. Electrospray ionization (ESI) high-resolution mass spectrometry (HR-MS) data were measured on a Bruker micrOTOF II instrument.

General procedure

An emulsion of salicylaldehyde **1** (3 mmol), *N*,*N*′-dimethylbarbiturate (6 mmol, 1 g) and *p*-TsOH (52 mg) in *n*-propanol (3 mL) was stirred under reflux for 15 min. After cooling, the resultant precipitate was filtered, washed with water (2×5 mL) and dried under reduced pressure to give pure compound **1a–h**.

5-(1,3-Dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1a) White solid; yield 1.18 g (99%); mp 236–237°C (Lit. [23]: mp 236°C); ^{1}H NMR: δ 2.87 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 3.97 (d, *J* = 2.4 Hz, 1H, CH), 4.83 (d, *J* = 2.4 Hz, 1H, CH), 7.11 (d, *J* = 7.3 Hz, 1H, Ar), 7.24 (t, *J* = 7.3 Hz, 1H, Ar), 7.11 (d, *J* = 7.3 Hz, 1H, Ar), 7.39 (t, *J* = 7.3 Hz, 1H, Ar).

1,3-Dimethyl-5-(1,3,8-trimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1b) White solid; yield 1.17 g (95%); mp 196–198°C; ^{1}H NMR: δ 2.22 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 3.87 (d, *J* = 2.2 Hz, 1H, CH), 4.88 (d, *J* = 2.2 Hz, 1H, CH), 6.85 (s, 1H, Ar), 7.12–7.17 (m, 2H, Ar); ^{13}C NMR: δ 20.2, 27.7 (2C), 27.8, 28.8, 36.6, 54.2, 85.2, 116.3, 119.1, 127.9, 129.9, 135.2, 147.2, 149.9, 151.2, 154.2, 161.2, 166.9, 167.5; IR: ν 2957, 1697, 1639, 1593, 1490, 1373, 1259, 1105, 978, 754 cm^{-1}; MS: *m*/*z* 412 ([M$^+$], 6), 273 (6), 257 (100), 200 (34), 156 (8%). HR-MS. Calcd for [M + Na$^+$]: *m*/*z* 435.1275, found: *m*/*z* 435.1270.

5-(9-Methoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1c) White solid; yield 1.27 g (98%); mp 250–252°C; ^{1}H NMR: δ 2.83 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 3.92 (d, *J* = 2.4 Hz, 1H, CH), 4.75 (d, *J* = 2.4 Hz, 1H, CH), 6.59 (d, *J* = 7.9 Hz, 1H, Ar), 7.05 (d, *J* = 7.4 Hz, 1H, Ar), 7.12 (dd, J_1 = 7.9 Hz, J_2 = 7.4 Hz, 1H, Ar); ^{13}C NMR: δ 27.6, 27.7, 28.0, 28.9, 36.0, 54.1, 56.2, 85.3, 112.1, 118.5, 120.6, 125.7, 138.6, 147.4, 149.9, 151.1, 154.0, 161.2, 167.0, 167.4; IR: ν 2947, 1670, 1639, 1585, 1485, 1381, 1229, 1101, 989, 784 cm^{-1}; MS: *m*/*z* 428 ([M$^+$], 9), 273 (100), 216 (32), 201 (7), 173 (7), 42 (5). HR-MS. Calcd for [M + Na$^+$]: *m*/*z* 451.1224, found: *m*/*z* 451.1225.

5-(7-Chloro-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1d) White solid; yield 1.29 g (99%); mp 260–262°C; ^{1}H NMR: δ 2.94 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 4.06 (d, *J* = 1.8 Hz, 1H, CH), 4.85 (d, *J* = 1.8 Hz, 1H, CH), 7.19 (d, *J* = 2.0 Hz, 1H, Ar), 7.38 (d, *J* = 8.7 Hz, 1H, Ar), 7.47 (dd, J_1 = 2.0 Hz, J_2 = 8.7 Hz, 1H, Ar); ^{13}C NMR: δ 27.7 (2C), 27.9, 28.9, 35.2, 54.4, 85.0, 118.6, 122.2, 127.7, 129.2, 133.6, 148.2, 149.9, 151.2, 154.0, 161.1, 166.7, 167.2; IR: ν 2950, 1677, 1639, 1571, 1449, 1322, 1249, 1113, 826, 755 cm^{-1}; MS: *m*/*z* 434 ([M$^+$], 2, Cl^{37}), 432 ([M$^+$], 7, Cl^{35}), 277 (100), 220 (23), 177 (5), 42 (5). HR-MS. Calcd for [M + Na$^+$] (Cl^{35}): *m*/*z* 455.0729, found: *m*/*z* 455.0725. Calcd for [M + Na$^+$] (Cl^{37}): *m*/*z* 457.0701, found: *m*/*z* 457.0698.

5-(7-Bromo-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1e) White solid; yield 1.42 g (98%); mp 276–278°C; ^{1}H NMR: δ 2.93 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 4.04 (d, *J* = 1.7 Hz, 1H, CH), 4.84 (d, *J* = 1.7 Hz, 1H, CH), 7.20 (d, *J* = 8.6 Hz, 1H, Ar), 7.33 (s, 1H, Ar), 7.59 (d, *J* = 8.6 Hz, 1H, Ar); ^{13}C NMR: δ 27.7 (2C), 27.9, 28.9, 35.3, 54.4, 85.0, 117.3, 118.9, 122.5, 130.6, 132.1, 148.6, 149.9, 151.1, 154.0, 161.1, 166.7, 167.3; IR: ν 2959, 1686, 1641, 1576, 1448, 1384, 1248, 1116, 977, 755 cm^{-1}; MS: *m*/*z* 478 ([M$^+$], 13, Br^{81}), 476 ([M$^+$], 13, Br^{79}), 363 (6), 232 (100), 264 (42), 242 (14), 185 (10), 114 (8), 69 (5), 42 (8%). HR-MS. Calcd for [M + Na$^+$] (Br^{79}): *m*/*z* 499.0224, found: *m*/*z* 499.0219. Calcd for [M + Na$^+$] (Br^{81}): *m*/*z* 501.0204, found: *m*/*z* 501.0198.

5-(1,3-Dimethyl-7-nitro-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1f) White solid; yield 1.28 g (96%); mp 266–268°C; ^{1}H NMR: δ 2.95 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 4.27 (m, 1H, CH), 5.03 (m, 1H, CH), 7.58 (d, *J* = 9.0 Hz, 1H, Ar), 8.06 (s, 1H, Ar), 8.26 (d, J_3 = 9.0 Hz, 1H, Ar); ^{13}C NMR: δ 27.7 (2C), 27.9, 29.0, 33.6, 54.3, 85.3, 118.0, 122.1, 124.2, 124.8, 128.5, 144.3, 149.8, 151.1, 153.6, 161.0, 166.7, 167.2; IR: ν 2964, 1695, 1645, 1582, 1525, 1460, 1385, 1254, 1091 cm^{-1}; MS: *m*/*z* 443 ([M$^+$], 7), 426 (7), 288 (100), 242 (10), 231 (31), 185 (30), 114 (7), 58 (5), 44 (15). HR-MS. Calcd for [M + Na$^+$]: *m*/*z* 466.0969, found: *m*/*z* 466.0965.

5-(7-Bromo-9-methoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-chromeno[2,3-*d*]pyri-midin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1g) White solid; yield 1.48 g (97%); mp 232–234°C; ^{1}H NMR: δ 2.94 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.02 (m, 1H, CH), 4.79 (m, 1H, CH), 6.86 (s, 1H, Ar), 7.32 (s, 1H, Ar); ^{13}C NMR: δ 27.7, 27.9 (2C), 28.9, 35.3, 54.2, 56.8, 85.0, 115.2, 117.2, 121.2, 122.7, 138.1, 148.3, 149.8, 151.1, 153.7, 161.1, 166.7, 167.2; IR: ν 2946, 1693, 1669, 1637, 1579, 1481, 1379, 1229, 1104, 628 cm^{-1}; MS: *m*/*z* 508 ([M$^+$], 5, Br^{81}), 506 ([M$^+$], 5, Br^{79}), 370 (8), 351 (100), 294 (15), 42 (6%). HR-MS. Calcd for [M + Na$^+$] (Br^{79}): *m*/*z* 529.0329, found: *m*/*z* 529.0325. Calcd for [M + Na$^+$] (Br^{81}): *m*/*z* 531.0310, found: *m*/*z* 531.0307.

5-(7,9-Dichloro-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1h) White solid; yield 1.35 g (96%); mp 220–222°C; ^{1}H NMR: δ 2.99 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.20 (s, 3H,

CH_3), 3.48 (s, 3H, CH_3), 4.15 (m, 1H, CH), 4.91 (m, 1H, CH), 7.23 (s, 1H, Ar), 7.79 (s, 1H, Ar); ^{13}C NMR: δ 27.8, 28.0 (2C), 29.0, 34.3, 54.5, 85.3, 121.9, 124.3, 126.9, 129.1, 129.5, 144.4, 149.7, 151.2, 153.5, 161.0, 166.6, 167.0; IR: ν 2957, 1686, 1645, 1575, 1452, 1375, 1260, 1195, 851, 757 cm^{-1}; MS: 470 ([M$^+$], 1, $Cl^{37}Cl^{37}$), 468 ([M$^+$], 4, $Cl^{35}Cl^{37}$), 466 ([M$^+$], 6, $Cl^{35}Cl^{35}$), 351 (4), 311 (100), 254 (41), 211 (15), 199 (11), 148 (8), 69 (9), 42 (15%). HR-MS. Calcd for ([M + Na$^+$] ($Cl^{35}Cl^{35}$): *m*/*z* 489.0339, found *m*/*z* 489.0337. Calcd for [M + Na$^+$] ($Cl^{37}Cl^{35}$): *m*/*z* 491.0311, found: *m*/*z* 491.0305. Calcd for [M + Na$^+$] ($Cl^{37}Cl^{37}$): *m*/*z* 493.0281, found: *m*/*z* 493.0292.

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References

[1] Thompson, L. A. Recent applications of polymer-supported reagents and scavengers in combinatorial, parallel, or multistep synthesis. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324–337.

[2] Nefzi, A.; Ostresh, J. M.; Houghten, R. A. The current status of heterocyclic combinatorial libraries. *Chem. Rev.* **1997**, *97*, 449–472.

[3] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade reactions in total synthesis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

[4] Padwa, A. Application of cascade processes toward heterocyclic synthesis. *Pure Appl. Chem.* **2003**, *75*, 47–62.

[5] Grondal, C.; Jeanty, M.; Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.* **2010**, *2*, 167–178.

[6] Narayan, S.; Muldoon, J.; Finn, M. J.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. 'On water': unique reactivity of organic compounds in aqueous suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279.

[7] Demchuk, D. V.; Elinson, M. N.; Nikishin, G. I. 'On water' Knoevenagel condensation of isatins with malononitrile. *Mendeleev Commun*. **2011**, *21*, 224–225.

[8] Elinson, M. N.; Nasybullin, R. F.; Ryzhkov, F. V.; Egorov, M. P. Solvent-free and 'on-water' multicomponent assembling of salicylaldehydes, malononitrile and 3-methyl-2-pyrazolin-5-one: a fast and efficient route to the 2-amino-4-(1*H*-pyrazol-4-yl)-4*H*-chromene scaffold. *C. R. Chimie* **2014**, *17*, 437–442.

[9] Sarkar, A.; Santra, S.; Kundu, S. K.; Hajra, A.; Zyryanov, G. V.; Chupakhin, O. N.; Charushin, V. N.; Majee, A. A decade update on solvent and catalyst-free neat organic reactions: a step forward towards sustainability. *Green Chem*. **2016**, *18*, 4475–4525.

[10] Elinson, M. N.; Ryzhkov, F. V.; Nasybullin, R. F.; Zaimovskaya, T. A.; Egorov, M. P. Sodium acetate catalyzed multicomponent approach to medicinally privileged 2-amino-4*H*-chromene scaffold from salicylaldehydes, malononitrile and cyanoacetates. *Mendeleev Commun*. **2014**, *24*, 170–172.

[11] Vereshchagin, A. N.; Elinson, M. N.; Nasybullin, R. F.; Ryzhkov, F. V.; Bobrovsky, S. I.; Bushmarinov, I. S.; Egorov, M. P. One-pot 'on-solvent' multicomponent protocol for the synthesis of medicinally relevant 4*H*-pyrano[3,2-*c*]quinoline scaffold. *Helv. Chim. Acta* **2015**, *98*, 1104–1114.

[12] Bräse, S. ed. Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation. RSC: Cambridge, 2015.

[13] Johns, M. W. Sleep and hypnotic drugs. *Drugs* **1975**, *9*, 448–478.

[14] Uhlmann, C.; Fröscher, W. Low risk of development of substance dependence for barbiturates and clobazam prescribed as antiepileptic drugs: results from a questionnaire study. *CNS Neurosci. Ther.* **2009**, *15*, 24–31.

[15] Naguib, F. N. M.; Levesque, D. L.; Eng-Chi, W.; Panzica, R. P.; El Kouni, M. H. 5-Benzylbarbituric acid derivatives, potent and specific inhibitors of uridine phosphorylase. *Biochem. Pharmacol.* **1993**, *46*, 1273–1283.

[16] Grams, F.; Brandstetter, H.; D'Alo, S.; Geppert, D.; Krell, H. W.; Leinert, H.; Livi, V.; Menta, E.; Oliva, A.; Zimmermann, G. Pyrimidine-2,4,6-triones: a new effective and selective class of matrix metalloproteinase inhibitors. *Biol. Chem.* **2001**, *382*, 1277–1285.

[17] Maquoi, E.; Sounni, N. E.; Devy, L.; Olivier, F.; Frankenne, F.; Krell, H.-W.; Grams, F.; Foidart, J.-M.; Noël, A. Anti-invasive, antitumoral, and antiangiogenic efficacy of a pyrimidine-2,4,6-trione derivative, an orally active and selective matrix metalloproteinases inhibitor. *Clin. Cancer Res.* **2004**, *10*, 4038–4047.

[18] Hadfield, J. A.; Pavlidis, V. H.; Perry, P. J.; McGown, A. T. Synthesis and anticancer activities of 4-oxobenzopyrano[2,3-*d*] pyrimidines. *Anti-Cancer Drugs* **1999**, *10*, 591–595.

[19] El-Agrody, A. M.; Halawa, A. H.; Fouda, A. M.; Al-Dies, A.-A. M. Novel chromeno[2,3-*d*]pyrimidines-design, synthesis and antioxidant activity. *Lett. Drug Des. Discov.* **2017**, *14*, 763–772.

[20] Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Impicciatore, M.; Ballabeni, V.; Barocelli, E. Synthesis antiplated, and antithrombic activities of new 2-substitued benzopyrano[4,3-*d*]pyrimidin-4-cycloamines and 4-amino/cycloamino-benzopyrano[4,3-*d*]pyrimidin-5-ones. *Bioorg. Med. Chem*. **2006**, *14*, 121–130.

[21] Bruno, O.; Brullo, C.; Schenone, S.; Ranise, A.; Bondavalli, F.; Barocelli, E.; Tognolini, M.; Magnanini, F.; Ballabeni, V. Progress in 5*H*-benzopyrano[4,3-*d*]pyrimidin-5-amine series: 2-methoxy derivatives effective as antiplatelet agents with analgesicactivity. *Farmaco* **2002**, *57*, 753–758.

[22] Umamahesh, B.; Mandlimath, T. R.; Sathiyanarayanan, K. I. A novel, facile, rapid, solvent free protocol for the one pot green synthesis of chromeno[2,3-*d*]pyrimidines using reusable nano $ZnAl_2O_4$ – a NOSE approach and photophysical studies. *RSC Adv.* **2015**, *5*, 6578–6597.

[23] Eiden, F.; Gerstlauer C. Darstellung und reaktionen von formyltetrahydrocannabinol-derivaten. *Arch. Pharm*. **1982**, *315*, 551–561.

[24] Zooroh, H. H.; Abou-El Zahab, M. M.; Mamdouh Abdel-Mogib, M.; Ismail, M. A. Peculiar reaction behaviour of barbituric acid derivatives towards aromatic amines. *Tetrahedron* **1996**, *52*, 10147–10158.

[25] Naya, S.; Masashi Miyagawa, M.; Makoto Nitta, M. Novel photoinduced oxidative cyclization of 1,3-dimethyl-5-(1-arylmethylidene)pyrimidine-2,4,6(1,3,5*H*)-triones: synthesis and properties of areno[5,6]pyrano[2,3-*d*]pyrimidine-2,4(1,3*H*)-dionylium ions and their photo-induced autorecycling oxidizing reaction toward some amines. *Tetrahedron* **2005**, *61*, 4919–4930.

[26] Patil, J. D.; Korade, S. N.; Pore, D. M. 1,1′-Sulfinyldipyridinium bis (hydrogen sulfate) ionic liquid: synthesis and application in the temperature-influenced synthesis of novel pyranopyrimidinediones and pyranopyrimidinetriones. *RSC Adv.* **2014**, *4*, 50449–50455.

[27] Elinson, M. N.; Vereshchagin, A. N.; Stepanov, N. O.; Belyakov, P. A.; Nikishin, G. I. Cascade assembly of *N*,*N*′-dialkylbarbituric

acids and aldehydes: a simple and efficient one-pot approach to the substituted 1,5-dihydro-2*H*,2′*H*-spiro(furo[2,3-*d*] pyrimidine-6,5′-pyrimidine)-2,2′,4,4′,6′(1′*H*,3*H*,3′*H*)-pentone framework. *Tetrahedron Lett*. **2010**, *51*, 6598–6601.

[28] Elinson, M. N.; Vereshchagin, A. N.; Stepanov, N. O.; Zaimovskaya, T. A.; Merkulova, V. M.; Nikishin, G. I. 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. *Tetrahedron Lett*. **2010**, *51*, 428–431.

[29] Elinson, M. N.; Gorbunov, S. V.; Vereshchagin, A. N.; Nasybullin, R. F.; Goloveshkin, A. S.; Bushmarinov, I. S.; Egorov, M. P. Chemical and electrocatalytic cascade cyclization of salicylaldehyde with three molecules of malononitrile: 'one-pot' simple and efficient way to the chromeno[2,3-*b*]pyridine scaffold. *Tetrahedron* **2014**, *70*, 8559–8563.

[30] Elinson, M. N.; Feducovich, S. K.; Stepanov, N. O.; Vereshchagin, A. N.; Nikishin, G. I. A new strategy of the chemical route to the cyclopropane structure: direct transformation of benzylidenemalononitriles and malononitrile into 1,1,2,2-tetracyanocyclopropanes. *Tetrahedron* **2008**, *64*, 708–713.

[31] Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Belyakov, P. A.; Barba, F.; Batanero, B. General non-catalytic approach to spiroacenaphthylene heterocycles: multicomponent assembling of acenaphthenequinone, cyclic CH-acids and malononitrile. *Tetrahedron* **2012**, *68*, 5833–5837.

[32] Elinson, M. N.; Merkulova, V. M.; Ilovaisky A. I.; Nikishin, G. I. Cascade assembling of isatins and barbituric acids: facile and efficient way to 2*H*-dispiro[indole-3,5-furo[2,3-*d*]pyrimidine-6,5-pyrimidine]-2,2,2,4,4,6-(1*H*,1*H*,1*H*,3*H*,3*H*)-hexone scaffold. *J. Heterocyclic. Chem*. **2013**, *50*, 1236–1241.

[33] Elinson, M. N.; Nasybullin, R. F.; Sokolova, O. O.; Zaimovskaya, T. A.; Egorov, M. P. Non-catalytic multicomponent rapid and efficient approach to 10-(2,4,6-trioxohexahydropyrimidin-5-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones from salicylaldehydes, dimedone, and barbituric acids. *Monatsh. Chem*. **2015**, *146*, 1689–1694.

[34] Elinson, M. N.; Merkulova, V. M.; Ilovaisky, A. I.; Barba, F.; Batanero, B. Electrocatalytic tandem Knoevenagel-Michael addition of barbituric acids to isatins: facile and efficient way to substituted 5,5′-(2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl) bis(pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione) scaffold. *Electrochim. Acta* **2011**, *56*, 8219–8223.