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On water noncatalytic tandem Knoevenagel–Michael reaction of aldehydes, *N,N′*-dimethylbarbituric acid and cyclohexane-1,3-diones

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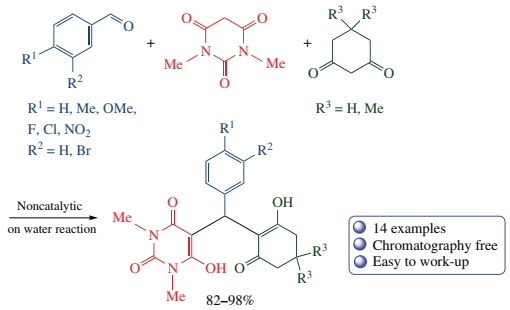
Heating aldehydes, *N,N′*-dimethylbarbituric acid and cyclohexane-1,3-diones in water results in fast formation of Knoevenagel–Michael adducts in 82–98% yields. This multicomponent process opens facile, efficient and environmentally benign way to the new functionalized [(2-hydroxy-6-oxocyclohex-1-en-1-yl)(aryl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones bearing both barbituric acid and cyclohexane-1,3-dione moieties separated by arylmethylene spacer, which are promising compounds for biomedical applications including analeptics, anti-AIDS and anticancer remedies.



Keywords: on water, noncatalytic, tandem reaction, aldehydes, *N,N′*-dimethylbarbiturates, cyclohexane-1,3-diones, Knoevenagel–Michael adduct.

Water plays an essential role in biological and chemical processes, though its use as a solvent in organic synthesis has been still limited.[1,2] Nevertheless, it was shown that certain organic reactions are greatly accelerated when they are carried out in vigorously stirred aqueous suspensions or emulsions.[3,4] The experiments with water-insoluble reactants or with a mixture of liquid and solid reagents as well as the corresponding yields reveal that the rates of these transformations are higher than those under solvent-free 'neat' or homogeneous conditions.[2] In last decades, the special term 'on water reactions' was introduced,[5–7] implying their realization in water dispersion with an unusual rate increase. This effect has been known for many years, and in 2005 Sharpless and co-workers presented its thorough investigation.[3]

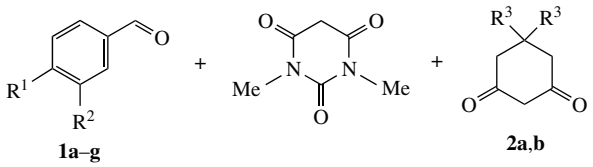
Recently, multicomponent reactions (MCRs) have become a widely accepted approach for the synthesis of heterocyclic compounds with diverse pharmaceutical applications. This method allowed one to increase the overall yield of complex organic products through a combination of several reactions in one-pot process and to decrease the number of labor consuming operations such as isolation and purification.[8–10] As well, to enhance the selectivity and efficiency of the desired complicated synthetic procedures, the application of the on water methodology was suggested[11–13] for MCRs of the compounds mixtures or emulsions in the absence of their full solubility. Considering these processes in terms of green chemistry, one can formulate that 'the best catalyst is no catalyst'.[14,15]

Hexahydropyrimidine-2,4,6-trione, or barbituric acid, represents a type of a privileged medicinal scaffold.[16] Many of its derivatives, typically 5-substituted, known as barbiturates, are drugs with the effect on the central nervous system.[17,18] The current attention to barbiturates arises also from their potential as anti-AIDS and anticancer agents.[19–21] Considering our interest in the implementation of the multicomponent synthesis of new heterocyclic systems bearing a barbiturate moiety, we have

Table 1 Multicomponent reaction of benzaldehyde **1a**, *N,N′*-dimethylbarbituric acid and cyclohexane-1,3-dione **2a**.[a]

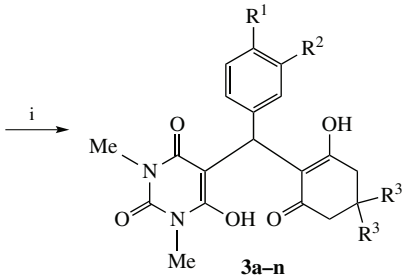
Entry	Solvent	Catalyst	Time/min	Temperature/°C	Yield of **3a**[b] (%)
1	H_2O	NaOAc	15	25	55[c]
2	H_2O	NaOAc	30	25	68
3	H_2O	NaOAc	60	25	80
4	H_2O	NaOAc	120	25	85
5	H_2O	–	15	25	48[c]
6	H_2O	–	30	25	56[c]
7	H_2O	–	60	25	70
8	H_2O	–	120	25	75
9	H_2O	–	3	60	62
10	H_2O	–	5	60	73
11	H_2O	–	15	60	92
12	H_2O	–	30	60	88
13	EtOH	NaOAc	15	25	55[c]
14	EtOH	NaOAc	30	25	69
15	EtOH	NaOAc	60	25	80
16	EtOH	NaOAc	120	25	81
17	EtOH	–	60	25	32[c]
18	EtOH	–	120	25	75
19	EtOH	–	15	78	54[c]
20	EtOH	–	30	78	82

[a] Benzaldehyde **1a** (5 mmol), *N,N′*-dimethylbarbituric acid (5 mmol) and cyclohexane-1,3-dione **2a** (5 mmol) were stirred in water (20 ml) or EtOH (10 ml) with or without catalyst (10 mol%) and/or heating. [b] Isolated yield. [c] NMR data.



1a–g **2a**,**b**

a $R^1 = R^2 = H$ **e** $R^1 = Cl$, $R^2 = H$ **a** $R^3 = H$
b $R^1 = Me$, $R^2 = H$ **f** $R^1 = H$, $R^2 = Br$ **b** $R^3 = Me$
c $R^1 = OMe$, $R^2 = H$ **g** $R^1 = NO_2$, $R^2 = H$
d $R^1 = F$, $R^2 = H$



3a–n

a $R^1 = R^2 = R^3 = H$ (92%) **h** $R^1 = R^2 = H$, $R^3 = Me$ (95%)
b $R^1 = Me$, $R^2 = R^3 = H$ (84%) **i** $R^1 = R^3 = Me$, $R^2 = H$ (90%)
c $R^1 = OMe$, $R^2 = R^3 = H$ (82%) **j** $R^1 = OMe$, $R^2 = H$, $R^3 = Me$ (86%)
d $R^1 = F$, $R^2 = R^3 = H$ (90%) **k** $R^1 = F$, $R^2 = H$, $R^3 = Me$ (87%)
e $R^1 = Cl$, $R^2 = R^3 = H$ (88%) **l** $R^1 = Cl$, $R^2 = H$, $R^3 = Me$ (89%)
f $R^1 = R^3 = H$, $R^2 = Br$ (83%) **m** $R^1 = H$, $R^2 = Br$, $R^3 = Me$ (85%)
g $R^1 = NO_2$, $R^2 = R^3 = H$ (85%) **n** $R^1 = NO_2$, $R^2 = H$, $R^3 = Me$ (98%)

Scheme 1 *Reagents and conditions*: i, water, 60 °C, 15 min.

developed several types of one-pot transformations of carbonyl compounds, barbiturates and CH-acids.[22–24]

In this work, we report our results on the new one-pot on water noncatalytic transformation of benzaldehydes **1**, *N*,*N*′-dimethylbarbituric acid and cyclohexane-1,3-diones **2a**,**b** into [(aryl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **3a**–**n** (Scheme 1, Table 1).

It is known that the on water methods have distinct advantages[25] over the usual 'in solvent' methods, especially when they are realized in a noncatalytic version.[26] Thus, at the beginning of our research, the synthesis of 2-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(phenyl)methyl]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **3a** starting from benzaldehyde **1a**, *N*,*N*′-dimethylbarbituric acid and cyclohexane-1,3-dione **2a** was attempted under the on water reaction conditions (Table 1, entries 1–12).

The use of NaOAc as a catalyst under the on water conditions with 15–120 min reaction time and without heating led to 55–85% yields of product **3a** (Table 1, entries 1–4).

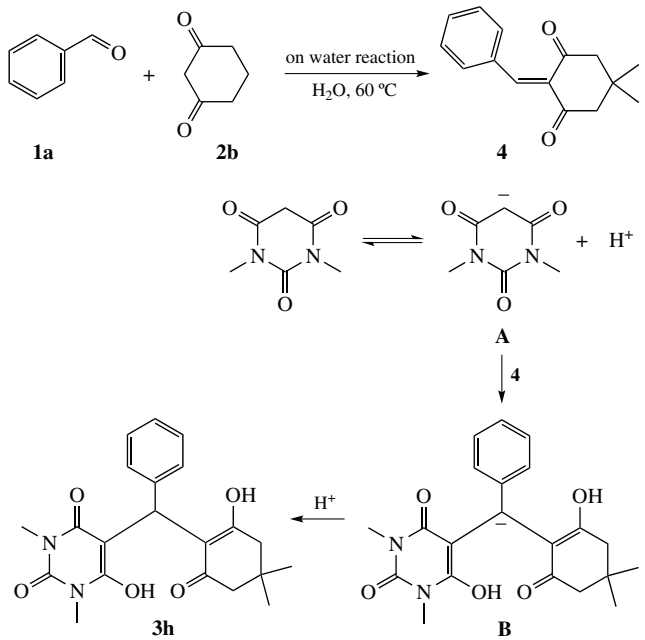
Under the same conditions without catalyst, compound **3a** was formed in slightly lower yield (48–75%) within 15–120 min (entries 5–8). The best results were obtained under the on water conditions with heating (entries 9–12), compound **3a** was isolated in 92% yield after 15 min reaction time. In ethanol solution this reaction was found to proceed with lower yields (entries 13–20).

Using the optimized reaction conditions, namely heating in water at 60° C for 15 min without a catalyst, we obtained the new substituted [(aryl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)methyl]-pyrimidine-2,4(1*H*,3*H*)-diones **3a**–**n** in 82–96% yields (Scheme 1).† The structures of all new compounds were confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy, mass spectrometry and elemental analysis (see Online Supplementary Materials).

Earlier, five representatives of 5-[(aryl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)methyl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones were synthesized *via* the reaction of 5-arylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones with 5,5-dimethylcyclohexane-1,3-dione by refluxing in absolute ethanol for 4–6 h in 65–70% yields.[27] As well, 5-[(4-fluorophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione was prepared starting from 4-fluorobenzaldehyde, *N*,*N*′-dimethylbarbituric acid and cyclohexane-1,3-dione in the presence of diethylamine (125 mol%) as a catalyst.[28]

With all these results and taking into consideration the known data on the multicomponent tandem Knoevenagel–Michael reaction,[29,30] the following mechanism for the noncatalytic multicomponent transformation of aldehydes **1a**–**g**, *N*,*N*′-dimethylbarbituric acid and cyclohexane-1,3-diones **2a**,**b** into compounds **3a**–**n** has been proposed (Scheme 2), as exemplified by starting reactants **1a** and **2b**. At the first step, the formation of Knoevenagel adduct **4** from benzaldehyde **1a** and dimedone **2b** occurs. Then a nucleophilic attack of *N*,*N*′-dimethylbarbiturate anion **A** on Knoevenagel adduct **4** results in the anion **B** generation followed by protonation and formation of the final compound **3h**.

In summary, the new fast and efficient multicomponent on water noncatalytic reaction of aldehydes, *N*-alkyl barbiturates and cyclohexane-1,3-diones leads to earlier unknown substituted [(aryl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones in 82–98% yields. This one-pot process



1a **2b** **4** **A** **3h** **B**

Scheme 2

† *Synthesis of compounds* **3a**–**n** *(general procedure).* The mixture of benzaldehyde **1** (5 mmol), *N*,*N*′-dimethylbarbituric acid (5 mmol, 0.78 g), and cyclohexane-1,3-dione **2a** or **2b** (5 mmol) in water (20 ml) was stirred at 60 °C for 15 min. When the reaction was completed, the solid was filtered off, washed by cold EtOH (2×3 ml) and in some cases additionally purified by recrystallization from EtOH.

*6-Hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(phenyl)methyl]-1,3-dimethylpyrimidine-2,4(1*H,*3*H)*-dione* **3a**. Yield 1.71 g (96%), mp 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.04–2.10 (m, 2H, CH_2), 2.33–2.52 (m, 2H, CH_2), 2.62–2.73 (m, 2H, CH_2), 3.38 (s, 3H, Me), 3.47 (s, 3H, Me), 5.57 (s, 1H, CH), 7.11–7.34 (m, 5H, Ar), 8.10 (br. s, 1H, OH), 13.15 (br. s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.9, 29.0, 29.2, 32.4, 33.6, 33.7, 92.3, 117.5, 126.3, 126.5 (2C), 128.3 (2C), 137.2, 150.8, 162.3, 164.7, 191.3, 193.6. MS *m*/*z* (%): 356 [M^+] (11), 312 (1), 257 (3), 243 (14), 199 (39), 156 (21), 129 (18), 102 (35), 56 (27), 42 (100). IR (KBr, ν/cm^{-1}): 2936, 2882, 1698, 1609, 1490, 1476, 1449, 1356, 1200, 882. Found (%): C, 63.95; H, 5.57; N, 7.75. Calc. for $C_{19}H_{20}N_2O_5$ (%): C, 64.04; H, 5.66; N, 7.86.

represents a simple approach to the products containing barbituric acid moiety as promising compounds for biomedical applications including analeptic, anti-AIDS and anticancer remedies. The procedure uses simple equipment and readily available starting compounds, it is realized easily and the isolation step is not complicated, the whole process being valuable in terms of environmentally benign diversity-oriented large scale reactions demand. With additional consideration of the mild reaction conditions and the short reaction time, these advantages make the proposed method a prospective one for the synthesis of new potential drug libraries.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.01.005.

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