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Four component tandem Knoevenagel–Michael strategy for the assembly of arylaldehydes, *N*,*N*′-dimethylbarbituric acid, 4-hydroxy-6-methyl-2*H*-pyran-2-one and morpholine into unsymmetrical scaffold with three different heterocyclic rings

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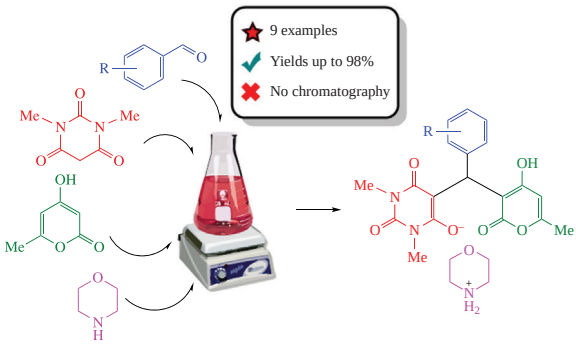
A new type of four component tandem Knoevenagel–Michael reaction has been found consisting in the assembly of benzaldehydes, *N*,*N*′-dimethylbarbituric acid, 4-hydroxy-6-methyl-2*H*-pyran-2-one and morpholine in alcohols, other organic solvents or water at room temperature without catalyst or any other additives, which results in the selective formation of unsymmetrical scaffold with three different heterocyclic rings in 63–98% yields. The crystal structure of morpholinium 5-[(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)(4-nitrophenyl)methyl]-1,3-dimethyl-2,6-dioxo-1,2,3,4-tetrahydropyrimidin-6-olate has been confirmed by X-ray diffraction.



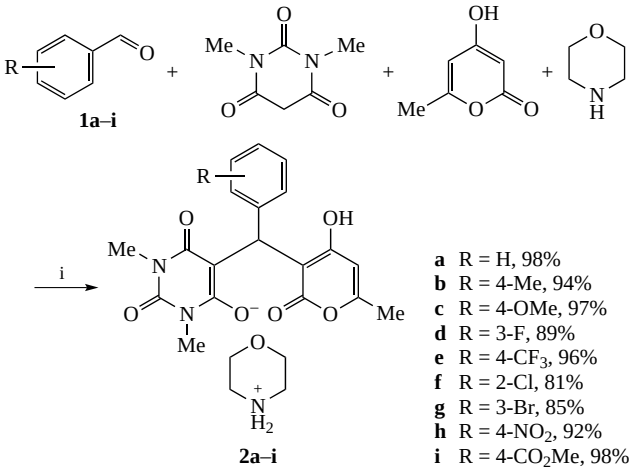
Keywords: multicomponent reaction, benzaldehydes, *N*,*N*′-dimethylbarbituric acid, 4-hydroxy-6-methyl-2*H*-pyran-2-one, morpholine, tandem Knoevenagel–Michael reaction.

Multicomponent reactions (MCRs) represent the main synthetic approach for diversity-oriented synthesis of products with high structural complexity in minimum steps.[1] However, complicated catalysts and the necessity of final purification diminish the advantages of MCRs as a green synthesis. Hence, an ideal synthetic protocol consists of simple mixing of reaction participants to achieve the desired product in one step, like in a tandem reaction as a combination of two or more simple steps in a specific order[2] with no isolation of intermediates and reduced pollution as a consequence. An example is the tandem Knoevenagel–Michael reaction known in classical organic chemistry,[2] which has been investigated till now.[3–7]

Privileged structures or scaffolds represent a class of molecules extensively used in drug discovery, which are capable of binding to multiple receptors with high affinity.[8,9] An example is barbiturates[10] employed as central nervous system (CNS) drugs, including sedative, anticonvulsant and anesthetic ones,[11–13] as well as for the treatment of the motor and sensory functions disorders.[14,15] Arenewed interest to barbiturates arose after it had been found that the pyrimidine-2,4,6-trione template was an efficient zinc-chelating moiety[16] and the corresponding derivatives demonstrated high selectivity toward matrix metalloproteinases responsible for cancer progression. Similarly, barbiturates reveal inhibition of uridine phosphorylase, which is found at an elevated level in some human tumor cells.[17] Also, barbiturates demonstrate inhibition of protein kinase C,[18] which represents a target for the treatment of immunological disorders, human immunodeficiency virus and rheumatoid arthritis as well as inflammatory diseases.[19] Another example of a privileged structure is the 2*H*-pyran-2-one one known for anti-HIV[20] and anticancer[21] properties of 4-hydroxy-2*H*-pyran-2-one derivatives as well as cardiotonic and anticancer effect of natural structures like bufalin.[22] Other 2*H*-pyran-2-one derivatives shows plant growth regulating,[23] antitumor[24] and HIV protease inhibition activities.[25] One more example of useful scaffolds for the development of CNS drugs is morpholine due to its well-balanced lipophilic−hydrophilic profile, pK_a value and a chair-like flexible conformation.[26] Doxapram,[27] phendimetrazine,[28] moclobemide,[29] reboxetine[30] and aprepitant[31] are some of active substances containing the morpholine fragment with their application as anxiolytics and/or antidepressants. Ionic heterocyclic scaffolds, particularly the barbituric ion pair ones, are also known as promising structures in drug design.[32]

Based on our experience in the tandem and multicomponent reactions resulting in complex heterocyclic compounds[33] and the biomedical applications of the heterocyclic ionic scaffolds, in this work we designed a convenient tandem Knoevenagel–Michael strategy for catalytic four component transformation of benzaldehydes **1a**–**i**, *N*,*N*′-dimethylbarbituric acid, 4-hydroxy-6-methyl-2*H*-pyran-2-one and morpholine into unsymmetrical ionic scaffold instances **2a**–**i** having three heterocyclic rings (Scheme 1 and Table 1).

To estimate the reaction conditions, we carried several runs using benzaldehyde **1a** and ethanol as a solvent (Table 1, entries 1–5). After 30 min as an optimal reaction time, product **2a** was obtained in 92% yield (Table 1, entry 3). Among other alcohols,



Scheme 1 *Reagents and conditions*: i, Pr^{n}OH, room temperature, 30 min.

Table 1 One-pot assembly of benzaldehyde **1a**, *N*,*N*′-dimethylbarbituric acid, 4-hydroxy-6-methyl-2*H*-pyran-2-one and morpholine.[a]

Entry	Solvent	Time/min	Yield of **2a** (%)[b]
1	EtOH	5	68
2	EtOH	15	85
3	EtOH	30	92
4	EtOH	60	91
5	EtOH	120	89
6	MeOH	30	93
7	Pr^{n}OH	30	98
8	Pr^{i}OH	30	86
9	MeCN	30	78
10	$CHCl_3$	30	87
11	H_2O	30	63

[a]Benzaldehyde **1a** (2 mmol), *N*,*N*′-dimethylbarbituric acid (2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol) and morpholine (2 mmol) were stirred in the solvent (4 ml) at room temperature. [b]Isolated by filtration.

n-propanol was found to be the best solvent with the formation of compound **2a** in 98% yield (Table 1, entries 6–8). The product was obtained in satisfactory yields in acetonitrile (78%), chloroform (87%) and even in water (63%) (Table 1, entries 9–11). Under the optimal conditions thus found, products **2a**–**i** were obtained in 81–98% yields (see Scheme 1).† The structure of new compounds **2a**–**i** was confirmed using ^{1}H, ^{13}C NMR and IR spectroscopy as well as mass spectrometry data and elemental analysis (see Online Supplementary Materials). For all the compounds only one set of signals was observed in their ^{1}H and ^{13}C NMR spectra. The structure of product **2h** was confirmed using X-ray diffraction (Figure 1 and Online Supplementary Materials).‡

† *General procedure for the synthesis of compounds* **2a**–**i**. A solution of arylaldehyde **1a**–**i** (2 mmol), *N*,*N*′-dimethylbarbituric acid (0.312 g, 2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.252 g, 2 mmol) and morpholine (0.174, 2 mmol) in ethanol (4 ml) was stirred at room temperature for 30 min. Then the product was filtered off, rinsed with an ice-cold ethanol–water (1 : 1, 2 ml) and dried *in vacuo* affording the corresponding compound **2**.

‡ *Crystal data for* **2h**. $C_{23}H_{26}N_4O_9$, M = 502.48, monoclinic, space group $P2_1/c$, a = 10.5365(2), b = 14.7314(2) and c = 15.4057(3) Å, β = 98.4420(10)°, V = 2365.32(7) Å^3, Z = 4, T = 296.15 K, D_{calc} = 1.411 g cm^{-3}, μ(MoKα) = 0.110 mm^{-1}, 26054 reflections measured (3.846° ⩽ 2θ ⩽ 61.09°), 7204 unique reflections (R_{int} = 0.0353, R_σ = 0.0358), which were used in all calculations. The final R_1 value was 0.0522 [$I > 2\sigma(I)$] and the wR_2 value was 0.1481.

CCDC 2046677 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.

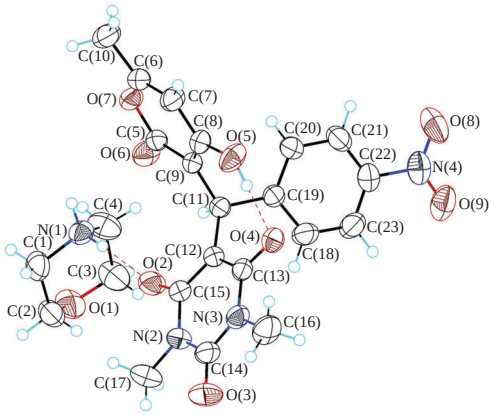
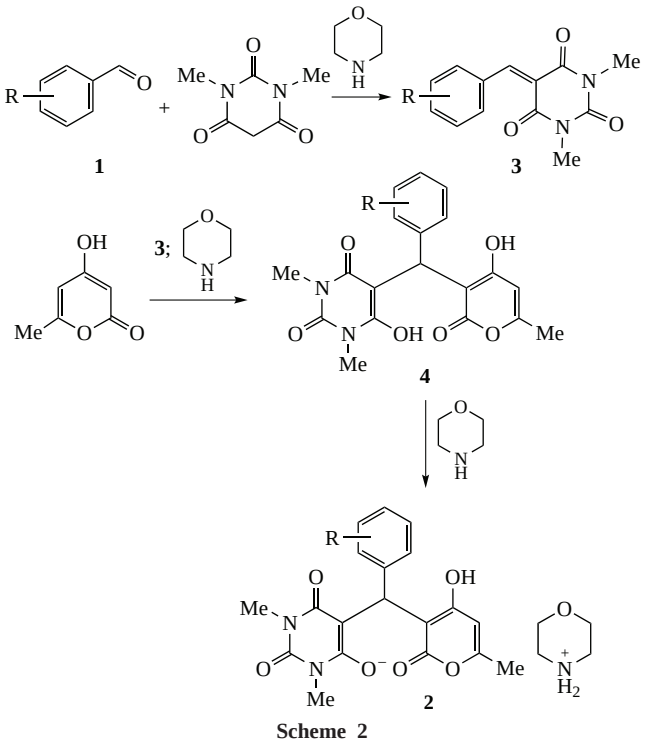


Figure 1 Molecular structure of compound **2h** with atoms represented by thermal displacement ellipsoids at 50% probability.



Scheme 2

Taking into consideration the known data on the tandem Knoevenagel–Michael reactions,[34] the following mechanism for the conversion investigated has been proposed (Scheme 2).

In the first step, the reaction of benzaldehyde and *N*,*N*′-dimethylbarbituric acid in the presence of morpholine results in Knoevenagel adduct **3**. The following addition of 4-hydroxy-6-methyl-2*H*-pyran-2-one affords unsymmetrical scaffold **4**. The final step is the formation of morpholinium 5-[(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)(aryl)methyl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-olate **2** after the reaction of compound **4** with morpholine.

Thus, the new type of four component tandem Knoevenagel–Michael reaction has been found, namely the assembly of benzaldehydes, *N*,*N*′-dimethylbarbituric acid, 4-hydroxy-6-methyl-2*H*-pyran-2-one and morpholine in alcohols, other organic solvents or water without catalyst or any other additives, resulting in the selective formation of earlier unknown substituted unsymmetrical scaffold with three different heterocyclic fragments in 63–98% yields. The procedure does not require complex equipment, heating or long reaction time and the isolation step is very simple. Thus, this method is valuable for environmentally benign diversity-oriented large-scale processes and the synthesis of new potential drug libraries. The products

may have 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.2021.09.035.

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