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Assembly of aldehydes and dimethylbarbituric acid into spirotricyclic furopyrimidines under the action of *N*-bromosuccinimide in water

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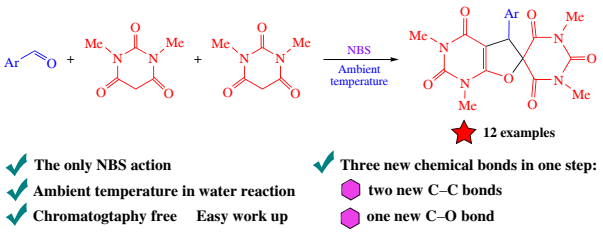
A new type of chemical one-pot tandem Knoevenagel–Michael reaction followed by the NBS-induced cyclization was discovered. The reaction of aromatic aldehydes with two molecules of *N*,*N*′-dimethylbarbituric acid in the presence of NBS in water at ambient temperature affords spirotricyclic furopyrimidine scaffold, namely, 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*)-pentones, in 90–98% yields.



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Carbon–carbon bond formations are one of the main processes in modern organic chemistry to construct the complex frameworks from common organic molecules.[1] Cascade transformations comprise at least two consecutive reactions so that each subsequent reaction occurs solely due to the chemical functionality formed in the previous step. Cascade reactions are useful for the facile and efficient generation of molecular complexity from simple and available reagents.[2]

On the other hand, heterocyclic compounds play significant role in modern drug discovery due to their unique structural and electronic properties, which allow them to interact with different receptors and enzymes.[3,4] The use of privileged structures or scaffolds is a rapidly developing area in medicinal chemistry since they are capable of binding to multiple receptors with high affinity. The exploitation of these molecules should allow medicinal chemists more rapidly discover biologically active compounds with a broad range of therapeutic applications.[5]

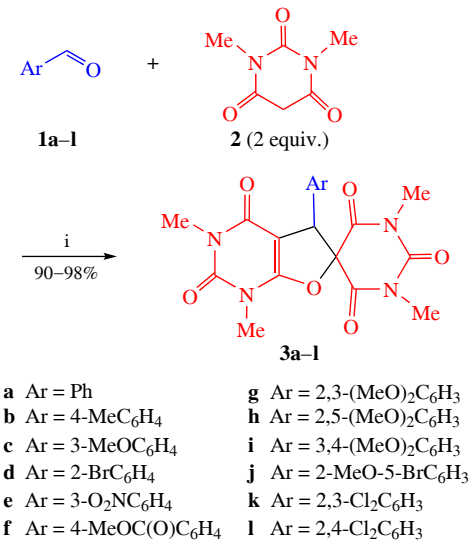
The barbiturate (pyrimidine-2,4,6-trione) scaffold is important for the development of pharmacologically active compounds, supramolecular host–guest architectures and functional materials.[6–11] A renewed interest to such compounds arose as the pyrimidinetrione unit was found to be an efficient zinc-chelating moiety.[12] Pyrimidinetrione derivatives have high selectivity toward matrix metalloproteinases responsible for cancer progression. Barbiturates demonstrated inhibition against protein kinase C, which is a target for therapeutic intervention in immunological disorders, the human immunodeficiency virus, and rheumatoid arthritis.[13]

Spiro compounds are considered as twisted structures in which at least two rings are connected *via* one common atom, and the two rings are generally perpendicular, so some spiro compounds possess axial chirality.[14] The interesting conformational aspects and structural implications of a biological system containing spiro compounds attract special attention.[15] An important group of heterocyclic spiro compounds is spiro dihydrofurans[16] which are frequently found as fundamental components in many kinds of natural products with biological significance and medicinal uses.[17]

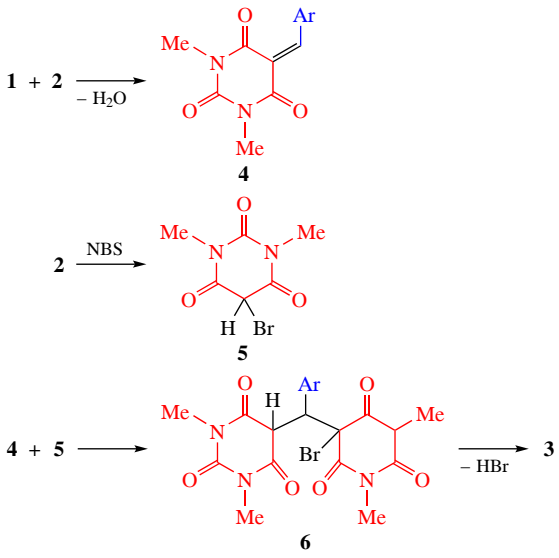
Barbiturate-incorporated spiro cycles constitute a class of chemical entities with a wide range of biological activities and important medical applications.[18] Spiro barbiturates have been established to exhibit neuropharmacological effects.[19] Recently, 1-phenyl-5,7-diazaspiro[2.5]octane-4,6,8-trione has been recognized as a tumor necrosis factor-alpha (TNF-α)-converting enzyme and matrix metalloproteinase inhibitor, and thus it could be utilized in the treatment of various inflammatory, infectious, immunological, or malignant diseases.[20]

Spirotricyclic compounds, including the spirotricyclic furopyrimidine framework, were synthesized by the tandem Knoevenagel–Michael reaction of aldehydes with two molecules of barbituric acid followed by further cyclization. Usually, a base–oxidant system was used to implement such type of cascade reaction. For example, MeONa–Br_2,[21] Et_3N–BrCN,[22] urotropine–bromine[23] action on aromatic aldehydes and barbituric derivatives led to the formation of spirotricyclic furopyrimidine framework in moderate to good yields. In the case of the urotropine–bromine system the final crystallization from ethanol was also needed.[23] Electrolysis of barbituric acids and aromatic aldehydes in ethanol in the presence of NaBr as a mediator in an undivided cell also led to the corresponding spiro products in good yields, with bromine formed at the anode and methoxy anions generated at the cathode having conducted the transformation.[24] The abovementioned procedures have their merits, however the facile, convenient and efficient tandem Knoevenagel–Michael method with the following cyclization is still in demand.

Considering our experience in cascade and multicomponent reactions with the formation of the new complex spiro heterocyclic compounds[25–27] and biomedical applications of spirotricyclic furopyrimidines, we herein designed a convenient cascade Knoevenagel–Michael process with a one-pot following chemical cyclization for direct assembling aldehydes and two



Scheme 1 *Reagents and optimum conditions*: i, NBS, H_2O, ambient temperature, 60 min.



Scheme 2

molecules of barbituric acid into substituted 5,6-dihydrofuro-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones, containing also spiro pyrimidine-2,4,6-trione fragment. For the oxidative cyclization agent, we used NBS. It should be noted that earlier we used base–molecular halogen system for the one-pot cascade transformation of alkylidenemalononitriles and malononitrile into substituted 1,1,2,2-tetracyanocyclopropanes.[28] The base–molecular halogen system was also employed for the synthesis of spirocyclopropylbarbiturates from two or three different molecules.[29,30]

N-Bromosuccinimide is one of the most efficient, selective, and versatile reagents in organic chemistry.[31] It is easy to handle, inexpensive, low toxic, readily available, usually more selective than bromine, and has been successfully employed for the new C–C, C–O, C–N and C–S bond formation.[31] In this research, we used the only NBS for direct assembling benzaldehyde **1a** and two molecules of *N*,*N*′-dimethylbarbituric acid **2** into spirotricyclic furopyrimidine **3a** in ethanol at ambient temperature (Scheme 1, Table 1, entries 1–5). Under these conditions, the better yield of product **3a** was achieved within 60 min (entry 4). In methanol, product **3a** was formed in lower yield (entry 6). The lower yields were also obtained with *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) (entries 7 and 8).

Surprisingly, the best, close to the theoretical, yield of **3a** (98%) was obtained in water (see Table 1, entry 9). A key underlying feature of the crucial role of water in biological and other systems is the hydrogen bonds that water molecules form among themselves in a largely tetrahedral manner.[32] The C–H activations on water have become one of the main research area nowadays.[33] The use of water as the reaction medium has other advantages, like ease of product isolation, high heat capacity and unique redox stability.[34] Under the optimal conditions thus found (water as a solvent, NBS as reagent and oxidant, 1 h reaction time at ambient temperature), compounds **3a–l** were formed in 90–98% yields (see Scheme 1). In all these cascade processes, after the end of the reaction, the reaction mixture was filtered, the solid was rinsed with an ice-cold ethanol/water solution (1 : 1), and dried under reduced pressure. The structure of all new compounds **3c**,**f**,**g–k** was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy, as well as mass spectrometry data.

Table 1 Optimization for the synthesis of spirotricyclic furopyrimidine **3a**.[a]

Entry	Oxidant	Solvent	*t*/min	Yield of **3a** (%)
1	NBS	EtOH	5	33
2	NBS	EtOH	15	53
3	NBS	EtOH	30	75
4	NBS	EtOH	60	87
5	NBS	EtOH	90	85
6	NBS	MeOH	60	84
7	NCS	EtOH	60	43
8	NIS	EtOH	60	68
9	NBS	H_2O	60	98
10	NBS	H_2O	30	77

[a] *Reaction conditions*: benzaldehyde **1a** (1 mmol), *N*,*N*′-dimethylbarbituric acid **2** (2 mmol), and NBS (1.2 mmol) were stirred in a solvent (5 ml) at ambient temperature.

Taking into consideration the above results and the data for the mechanisms of the transformation of carbonyl compounds and CH-acids into substituted cyclopropanes,[21,22] the mechanism for the cascade transformation of aldehydes **1** and two molecules of *N*,*N*′-dimethylbarbituric acid **2** into spirotricyclic furopyrimidines **3** was proposed (Scheme 2). In the first step, the condensation of aldehyde **1** with CH-acid **2** in water takes place with the formation of the Knoevenagel product **4** even in the absence of base, as was reported earlier.[35] The simultaneous bromination of **2** with NBS to give bromobarbituric derivative **5** occurs. Bromobarbituric derivative **5** is a reasonably strong CH-acid which can[36–38] furnish a sufficient concentration of its carbanion for the Michael addition to the Knoevenagel olefin **4**; this should afford adduct **6** and finally spirotricyclic furopyrimidine **3** upon the cyclization.

In conclusion, a new type of one-pot Knoevenagel–Michael reaction with the following NBS-induced cyclization was found: the direct transformation of aldehydes **1** and *N*,*N*′-dialkyl-barbituric acid affords substituted spiro[furo[2,3-*d*]-pyrimidine-6,5′-pyrimidine]-2,2′,4,4′,6′(1′*H*,3*H*,3′*H*)-pentones **3** in 90–98% yields. This one-pot cascade process carried out in water by the action of only NBS at ambient temperature is very efficient and convenient. Products **3** thus obtained from non-expensive starting materials seem useful for various biomedical applications. Mild and facile conditions of this one-pot procedure providing excellent yields along with a simple isolation represent strong advantages for the preparation of new potential drug libraries.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7844.

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