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PAPER

Stereoselective synthesis of medicinally relevant furo[2,3-*d*]pyrimidine framework by thermal rearrangement of spirocyclic barbiturates

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The new rearrangement of functionalised cyclopropanes was found: thermally initiated transformation of substituted 2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octanes in DMSO at 100 °C results in the formation of furo[2,3-*d*]pyrimidines in 50–75% yields. Similar results were obtained using [bmim][BF_4] as a solvent. NMR and single-crystal X-ray diffraction analysis indicate stereoselective formation of (5*R**,6*R**) isomers by thermal rearrangement of 2-aryl-1-cyano-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1-carboxylates.

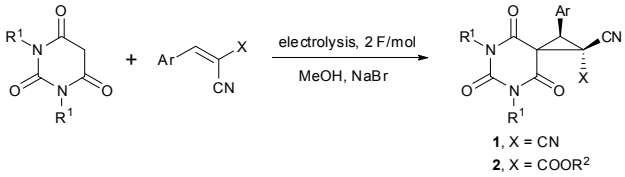
Introduction

The cyclopropane subunit plays a prominent role in organic chemistry. Its distinctive reactivity is caused by the strained structure and unique bonding characteristics which underlie a variety of chemical transformations available for the three-membered cycloalkanes. Cyclopropane and its derivatives are an efficient and powerful synthetic building blocks for the straightforward synthesis of diverse carbo- and heterocycles with molecular complexity.[1] Cyclopropanes with donor and acceptor substituents in vicinal position (donor–acceptor cyclopropanes) are popular in organic synthesis nowadays as a source of 1,3-dipoles generated from them in the presence of Lewis acids or upon heating.[1e-k,2]

Among different types of cyclopropane fragments a spirocyclopropyl moiety jointed with a heterocyclic counterpart has attracted particular attention due to its synthetic utility and wide number of pharmacological applications.[3] In particular, fused spirocyclopropyl heterocycles have been recognized as α-L-fucosidase,[3a] β- lactamase,[3b] and HIV-1 non-nucleoside reverse transcriptase inhibitors as well as diagnostic markers for the early detection of colorectal and hepatocellular cancers.[3c,d]

Barbituric acid is a versatile molecule for designing potential bioactive agents. A large number of substituted barbituric acid derivatives have been reported to exhibit a broad spectrum of biological properties like anticonvulsant,[4a] anaesthetic,[4b] antiparkinsonian,[4c] sedative and hypnotic.[4d,e] Spirobarbiturates have attracted special attention in the organic and pharmaceutical community due to the unique structural assembly and associated spectrum of biological activities.[5]

In a course of our studies on electrocatalytic synthesis of cyclopropane derivatives,[6] we recently reported an efficient stereoselective approach to the 4,6,8-trioxo-5,7-diazaspiro[2.5]octanes **1**,**2** (Scheme 1).[7] Donor-acceptor cyclopropanes **1**,**2** were isolated by direct filtration of the reaction mixture and did not require any further purification.



Scheme 1 Stereoselective electrocatalytic synthesis of 4,6,8-trioxo-5,7-diazaspiro[2.5]octanes.

The ever-growing importance of thermal cyclopropane rearrangements in various synthetic applications attests to uniqueness and convenience of methodology especially when the starting cyclopropane is more readily available than isomeric propene.[1a,8] Recently, we carried out stereoselective thermal isomerization of bis(spiropyrazolone)cyclopropanes into (4*Z*)-4-[(pyrazol-4-yl)methylene]pyrazolones.[9] A thorough literature search revealed that there are no precedents of thermal rearrangements of spirocyclic barbiturates containing cyclopropane ring.

Results and discussion

In the present study we report our results on the thermal rearrangement of spirocyclic barbiturates **1** (Scheme 2, Table 1 and 2) and **2** (Scheme 3, Table 3). In order to find optimal conditions, thermal rearrangement of 5,7-dimethyl-4,6,8-

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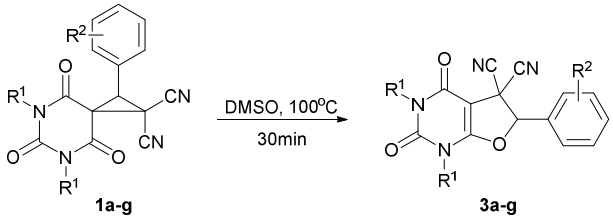
trioxo-2-phenyl-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile **1a** was selected as a model reaction (Table 1).



a R^1 = Me, R^2 = H
b R^1 = H, R^2 = H
c R^1 = Et, R^2 = H
d R^1 = Me, R^2 = 4-*t*Bu
e R^1 = Me, R^2 = 4-Me
f R^1 = Me, R^2 = 4-Cl
g R^1 = Me, R^2 = 3-Br

Scheme 2 Thermal rearrangement of 2-aryl-5,7-dialkyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles **1**.

a R^1 = H, R^2 = COOMe
b R^1 = H, R^2 = COOEt
c R^1 =4-*t*Bu, R^2 = COOEt
d R^1 = 4-Me, R^2 = COOMe
e R^1 =3-Br, R^2 = COOMe
f R^1 =4-Cl, R^2 = COOEt
g R^1 =4-F, R^2 = COOMe

Scheme 3 Stereoselective thermal rearrangement of alkyl (1*R**,2*S**)-1-cyano-2-aryl-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro [2.5]octane-1-carboxylates **2**.

Table 1 Thermal rearrangement of **1a** into **3a**.[a]

Entry	Solvent	Temperature (°C)	Time (min)	Conv. of **1a** (%) [b]
1	H_2O	100	30	0
2	EtOH	78	30	0
3	*n*-PrOH	97	30	12
4	EtOAc	77	30	0
5	MeCN	82	30	12
6	Toluene	110	30	15
7	DMF [c]	100	30	52
8	NMP [c]	100	30	75
9	**DMSO [c]**	**100**	**30**	**84**
10	**[BMim]BF_4 [d]**	**100**	**30**	**86**
11	DMSO [c]	100	15	50
12	DMSO [c]	100	60	65
13	DMSO [c]	50	30	0
14	DMSO [c]	150	30	73

[a] **1a** (1 mmol), solvent (10 mL), heating. [b] Selective conversion into **3a**, ^{1}H NMR data. [c] 0.5 mL of solvent. [d] 1 mmol of ionic liquid was used

Heating of **1a** in water or ethanol under reflux for 30 min did not result in any conversion of the starting compound probably due to its insolubility (Table 1, entries 1, 2). After 30 min under reflux conditions in 1-propanol **1a** was selectively converted into 1,3-dimethyl-2,4-dioxo-6-phenyl-1,2,3,4-tetrahydrofuro[2,3-*d*]pyri-midine-5,5(6*H*)-dicarbonitrile **3a** in 12% yield (entry 3). As for aprotic solvents, a solution of **1a** in ethyl under reflux acetate was unreactive; although in boiling acetonitrile or toluene the selective conversion into **3a** was observed in 12% and 15% yield, respectively (entries 4-6). A dramatic improvement was achieved with high-boiling polar aprotic solvents. Thus, heating **1a** at 100 °C in DMF resulted in formation of **3a** in 52% yield (entry 7). The use of more polar solvents, such as NMP or DMSO for 30 minutes at 100 °C resulted in 75% and 84% conversion of starting compound respectively and only 1,3-dimethyl-2,4-dioxo-6-phenyl-1,2,3,4-tetrahydro-furo[2,3-*d*]pyrimidine-5,5(6*H*)-dicarbonitrile **3a** was formed (entries 8, 9). Moreover, these conditions allowed a 20-fold decrease of the required amount of solvent. The 30 min heating in DMSO at 100 °C is an optimal condition. Both increase and decrease of temperature or time of procedure resulted in a drop of **3a** yield (entries 11-14).

It was also found that the rearrangement of **1a** into **3a** occurred with high selectivity (86%) using 1-butyl-3-methylimi-dazolium tetrafluoroborate [BMim]BF_4 as a solvent. The reco-very and reuse of the ionic liquid was examined. The reaction was then attempted in recovered ionic liquid. Marginal loss in the yield of **3a** was observed within five cycles (Fig 1).

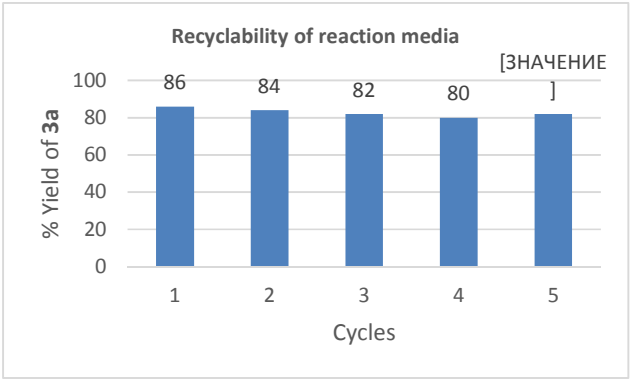


Fig. 1 Reusability of ionic liquid [BMim]BF_4.

Under the optimal conditions (0.5 mL of DMSO as a cheaper reagent than [BMim]BF_4 at 100 °C for 30 min) the thermal rearrangement of 2-aryl-5,7-dimethyl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitriles **1a-g** afforded the corresponding 6-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-furo[2,3-*d*]pyrimidine-5,5(6*H*)-dicarbonitriles **3a-g** in 50–66% yield (Scheme 2, Table 2).

Table 2 Thermal rearrangement of spirocyclopropylbarbiturates **1a-g** to the 5,6-dihydrofuro[2,3-*d*]pyrimidines **3a-g**.[a]

Entry	R^1	R^2	Product	Yield of **3** (%) [b]
1	Me	H	**3a**	66
2	H	H	**3b**	52
3	Et	H	**3c**	61
4	Me	4-*t*Bu	**3d**	58
5	Me	4-Me	**3e**	66
6	Me	4-Cl	**3f**	50
7	Me	3-Br	**3g**	62

[a] **1** (1 mmol), DMSO (0.5 mL), 100 °C; [b] Yield of isolated product.

The furo[2,3-*d*]pyrimidines possess important biological activities and are:

1. classical antifolates on dihydrofolate reductase (DHFR), thymidylate synthase (TS), and folylpolyglutamate synthetase (FPGS) as well as antitumor activity;[10]
2. multireceptor tyrosine kinase and dihydrofolate reductase inhibitors with antiangiogenic and antitumor activity;[11]
3. RTK and dihydrofolate reductase (DHFR) inhibitory activity in single molecules, as potential cytostatic and cytotoxic agents with antitumor activity.[12]

Also, the furo[2,3-*d*]pyrimidines are potent inhibitors of RIP1 (receptor interacting protein 1) kinase[13] and show anti-HCMV (human cytomegalovirus) activity.[14]

To widen the scope of the discovered method and evaluate its stereoselectivity aspects, the thermal rearrangement of alkyl (1*R**,2*S**)-1-cyano-5,7-dimethyl-4,6,8-trioxo-2-phenyl-5,7-diaza-spiro[2.5]octane-1-carboxylates **2a-g** was studied. Under the optimal conditions (0.5 mL of DMSO at 100 °C for 30 min), the thermal rearrangement of **2a-g** afforded the corresponding alkyl 6-aryl-5-cyano-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydrofuro[2,3-*d*]pyrimidine-5-carboxylates **4a-g** in 51–75% yields (Scheme 3, Table 3).δ+

Table 3 Stereoselective thermal rearrangement of spirocyclopropylbarbiturates **2a-g** to the 1,2,3,4,5,6-hexahydrofuro[2,3-*d*]pyrimidine-5-carboxylates **4a-g**[a]

Entry	R^1	R^2	Product	Yield of **4** (%) [b]
1	H	Me	**4a**	59
2	H	Et	**4b**	51
3	4-*t*Bu	Et	**4c**	55
4	4-Me	Me	**4d**	70
5	3-Br	Me	**4e**	73
6	4-Cl	Et	**4f**	75
7	4-F	Me	**4g**	56

[a] **2** (1 mmol), DMSO (0.5 mL), 100 °C; [b] Yield of isolated product.

It should be mentioned that the obtained furo[2,3-*d*]pyrimidines **4a-g** could exist as pairs of diastereoisomers with (5*R**,6*R**) or (5*R**,6*S**) configuration of the aryl and carbomethoxy substituents. However, in the NMR spectra of **4a-g**, only a single set of signals was present, assuming the stereoselective formation of individual diastereoisomers in the developed thermal rearrangement. The structure of furo[2,3-*d*]pyrimidine **4a** was further confirmed by a single-crystal X-ray diffraction study (Fig. 2). The X-ray diffraction data unambiguously support the (5*R**,6*R**) configuration for **4a**. Considering the facts given above, compounds **4a-g** should also possess (5*R**,6*R**) configuration.

A probable mechanism involved in the formation of products is outlined in Scheme 4. The C-C bond in cyclopropane undergoes a heterolytic bond cleavage upon heating in polar DMSO followed by closure in furan ring.

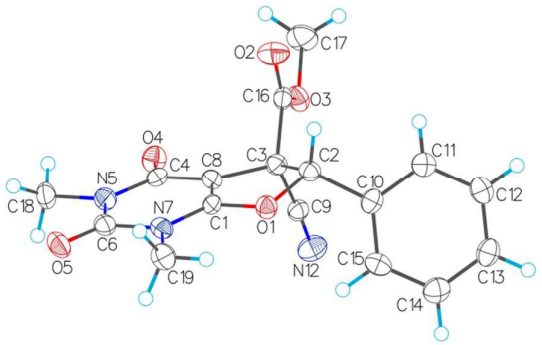
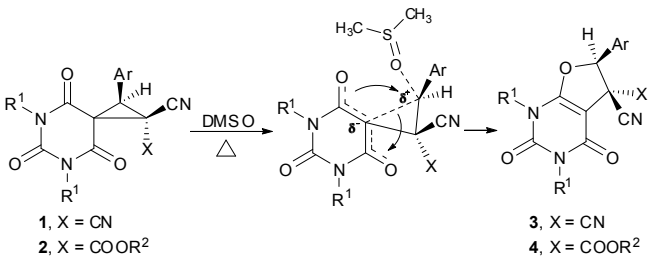


Fig. 2 X-ray crystal structure of **4a**.†



Scheme 4 Probable mechanistic pathway for the synthesis of furo[2,3-*d*]pyrimidines **3**, **4**.

Conclusions

In conclusion, we have developed an efficient approach to substituted furo[2,3-*d*]pyrimidines by thermal rearrangement of readily accessible spirocyclic barbiturates. The isomerization proceeds simply upon heating in DMSO, does not require any additional reagents or catalysts, and affords the 1,3-dimethyl-2,4-dioxo-6-phenyl-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidine-5,5(6*H*)-dicarbonitriles and individual diastereoisomers of alkyl (5*R**,6*R**)-5-aryl-6-cyano-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydrofuro [2,3-*d*]pyrimidine-6-carboxylates in good yields. The products are isolated by water-assisted precipitation directly from the reaction mixture.

Acknowledgements

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