Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 448–450

Mendeleev Communications

An expedient cyclization of polyfunctional (aryl)(pyrimidinyl)(pyranyl)methanes into spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine] scaffold

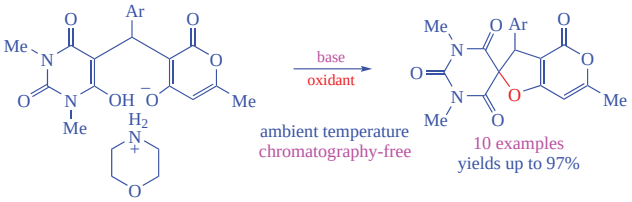
Michail N. Elinson,*[a] Anatoly N. Vereshchagin,[b] Yuliya E. Ryzhkova,[a] Kirill A. Karpenko,[a] Varvara M. Kalashnikova[a,b] and Mikhail P. Egorov[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: elinson@ioc.ac.ru*

[b] *D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2023.06.002

Spirocyclization of morpholinium 3-[(aryl)(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-6-methyl-2-oxo-2*H*-pyran-4-olate by the action of sodium acetate-*N*-bromosuccinimide system in ethanol at room temperature results in spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine] derivatives in 92–98% yields, the protocol allowing to avoid column chromatography purification. This new highly efficient and facile procedure is a convenient way to substituted unsymmetrical spiro scaffold containing pyrimidine-2,4,6-trione and 2,3-dihydro-4*H*-furo[3,2-*c*]pyran-4-one fragments promising for biomedical applications.



Keywords: cyclization, base–oxidant system, sodium acetate, *N*-bromosuccinimide, morpholinium salts, furo[3,2-*c*]pyrans, spiro[furo-[3,2-*c*]pyran-2,5′-pyrimidine], pyranones, pyrimidine-2,4,6-triones.

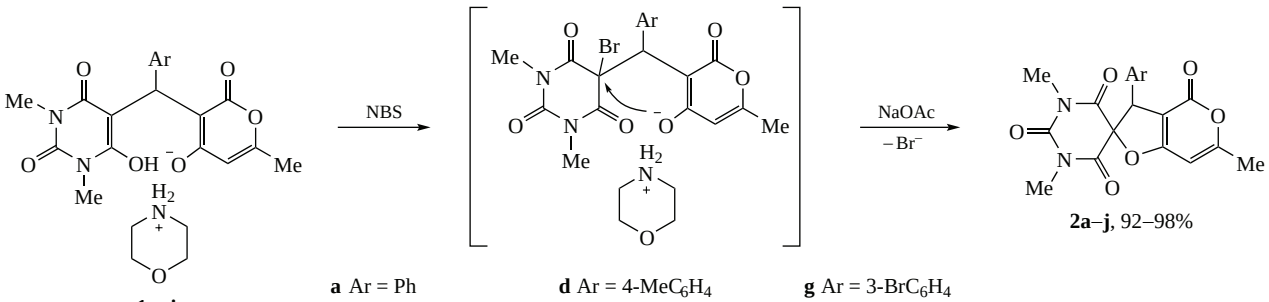
Over the past few years, the application of privileged structures has emerged as a useful way for the discovery of new biologically active compounds.[1] The scaffolds in question are mainly the rigid heterocyclic compounds with special orientation of functional substituents for target recognition. The creation of a facile and efficient method for selective synthesis of privileged scaffolds is an important goal of modern organic chemistry.[2]

Barbiturates are known as a privileged medicinal scaffold[3] in different central nervous system drugs, including sedatives, anticonvulsants, and anesthetics.[4] Nowadays, the new interest to barbiturates has arisen because their pyrimidine-2,4,6-trione template was found to be an efficient zinc-chelating moiety, and such derivatives demonstrated high selectivity toward matrix metalloproteinases responsible for cancer progression.[5] On the other hand, 2*H*-pyran-2-one is highly abundant in bacteria, microbial, plant, insect and animal systems. Its derivatives take part in defence against other organisms and serve as key biosynthetic intermediates or metabolites.[6] Derivatives of 4-hydroxy-2*H*-pyran-2-ones exhibit anti-HIV[7] and anticancer[8] properties. Among natural compounds with 2*H*-pyran-2-one fragment, bufalin is a cardiotonic steroid and anticancer agent.[9]

Spirocycles have been employed as core structures and are widely used in drug discovery.[10,11] Barbiturate-containing spirocycles are a class of chemical entities with a wide range of biological activities and important medical applications.[12] Thus, spiro barbiturates have been established to exhibit neuro-pharmacological effects.[13] They are inhibitors of matrix metalloproteinase 13 (MMP-13)[14] and dihydroorotate dehydrogenase (DHODase).[15]

Taking into consideration our experience in carrying out different types of chemical processes with the formation of spirocyclic heterocyclic compounds[16–18] and sufficient biomedical applications of spirocyclic barbiturates, we planned to design the efficient cyclization methodology for the one-step direct conversion of morpholinium 3-[(aryl)(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-6-methyl-2-oxo-2*H*-pyran-4-olates **1a**–**j** into non-symmetrically substituted 3-aryl-2′*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine]-2′,4,4′,6′-(1′*H*,3′*H*)-tetrones **2a**–**j** (Scheme 1). To find the best cyclization reaction conditions, we have performed the one-pot cyclization of model repersentative **1a** into product **2a** using various base–oxidant systems (Table 1).

Bromine is often used in oxidative cross dehydrogenation cyclization reactions providing formation of new carbon–carbon and carbon–heteroatom bonds.[19] Earlier we suggested base–molecular halogen system for direct synthesis of substituted 1,1,2,2-tetracyanocyclopropanes from alkylidenemalononitriles and malononitrile,[20,21] or from carbonyl compounds and malononitrile[22] as well as for direct assembling of spiro cyclopropane barbiturates from two or three different molecules.[23] Thus, initially we tested bromine as an oxidant and KOH, NaOH and NaOAc as bases (see Table 1, entries 1–3). Under these conditions, spiro[furo[3,2-*b*]pyran-2,5′-pyrimidine] **2a** was obtained in 47–55% yields. Molecular iodine has recently been recognized as an inexpensive, nontoxic, readily available reagent to affect different types of oxidative cyclization reactions.[24] In our experiments, iodine provided formation of product **2a** in 67–74% yields (entries 4, 5).



a Ar = Ph
b Ar = 2-MeC_6H_4
c Ar = 3-MeC_6H_4
d Ar = 4-MeC_6H_4
e Ar = 4-$MeOC_6H_4$
f Ar = 4-ClC_6H_4
g Ar = 3-BrC_6H_4
h Ar = 3-$O_2NC_6H_4$
i Ar = 4-$MeO_2CC_6H_4$
j Ar = 4-$F_3CC_6H_4$

Scheme 1 *Reagents and conditions*: **1a**–**j** (1 equiv.), NBS (1.2 equiv.), NaOAc (1 equiv.), EtOH, ambient temperature, 1 h.

Table 1 Oxidative cyclization of morpholinium 3-[(phenyl)(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-6-methyl-2-oxo-2*H*-pyran-4-olate **1a**.[a]

Entry	Oxidant	Base	Solvent	*t*/min	Yield of **2a** (%)[b]
1	Br_2	KOH	EtOH	60	47
2	Br_2	NaOH	EtOH	60	51
3	Br_2	NaOAc	EtOH	60	55
4	I_2	NaOH	EtOH	60	67
5	I_2	NaOAc	EtOH	60	74
6	NBS	NaOH	EtOH	60	80
7	NIS	NaOH	EtOH	60	73
8	NBS	NaOAc	EtOH	60	97
9	NBS	NaOAc	MeOH	60	86
10	NBS	NaOAc	Pr^iOH	60	81
11	NBS	NaOAc	EtOH	45	70
12	NBS	NaOAc	EtOH	30	46

[a] Reactant **1a** (1 mmol), base (1 mmol), oxidant (1.2 mmol), solvent (4 ml), ambient temperature. [b] Isolation of **2a** by filtration.

Sodium acetate is inexpensive, nontoxic and readily available catalyst for some organic reactions.[25,26] We have earlier found sodium acetate to catalyze stereoselective multicomponent cyclization of benzaldehydes, malononitrile and acetone into *cis*-2,6-diaryl-4-(dicyanomethylene)cyclohexane-1,1-dicarbonitriles.[27] In this research, NaOAc was found to be the best base in a base–oxidant system (see Table 1, entries 3, 5 and 8). *N*-Bromosuccinimide (NBS) is one of the most common and versatile reagents in organic chemistry[28] and has been employed in various reactions with new C–C,[29] C–O,[30] C–N[31] and C–S[32] bond formation. In this study, we found that NBS was the best oxidant for direct oxidative cyclization of morpholinium salt **1a** into spiro[furo[3,2-*b*]pyran-2,5′-pyrimidine] **2a** (entries 7 and 9–12). Under the best conditions (NaOAc–NBS oxidative system, EtOH as a solvent, ambient temperature, 60 min), product **2a** was obtained in 97% yield (entry 8).

Under the optimal conditions thus found, spiro[furo[3,2-*b*]-pyran-2,5′-pyrimidines] **2a**–**j** were formed in 92–98% yields (see Scheme 1).† In all these oxidative cyclization processes, after the end of the reaction, the reaction mixture was filtered, the solid product was rinsed with an ice-cold ethanol/water solution (1 : 1), and dried under reduced pressure to isolate the products **2a**–**j**. The structure of new compounds **2b**,**c**,**e**,**g**,**h**,**j** was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy as well as mass spectrometry data and elemental analysis. For all new compounds, only one set of signals was observed in ^{1}H and ^{13}C NMR spectra. Compounds **2a**,**d**,**f**,**i** were earlier obtained by electrochemical multicomponent assembly of aromatic aldehydes, dimethylbarbituric acid and 4-hydroxy-6-methyl-2*H*-pyran-2-one in 77–82% yields.[33]

With all above results and taking into consideration the data on cyclization reaction with the formation of spirocyclic compounds,[34] the following mechanism for oxidative cyclization of morpholinium salts **1** was proposed (see Scheme 1). At the first step of the process, morpholinium salt **1** is brominated with NBS to form of morpholinium 5-bromo-5-[(2-oxo-2*H*-pyran-3-yl)(aryl)methyl]-2,6-dioxopyrimidine. At the next step, intermolecular cyclization of the bromine-substituted compound leads to final spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine] derivative **2**.

In conclusion, the new type of cyclization reaction was found, *viz*. morpholinium 3-[(aryl)(1,3-dimethyl-2,4,6-trioxohexahydro-pyrimidin-5-yl)methyl]-6-methyl-2-oxo-2*H*-pyran-4-olates have been efficiently cyclized into spiro[furo[3,2-*c*]-pyran-2,5′-pyrimidines] using a new base–oxidant system AcONa/NBS. This new one-pot procedure is a facile and efficient way to the substituted unsymmetrical spiro scaffold containing both pyrimidine-2,4,6-trione and 2,3-dihydro-4*H*-furo[3,2-*c*]pyran-4-one fragments, which are promising compounds for different biomedical applications, including anticonvulsant, anti-AIDS agents and anti-inflammatory remedies. This facile procedure utilizes simple equipment and does not use heating, whereas the isolation step is chromatography-free. Thus, this new method is valuable from the viewpoint of diversity-oriented large-scale processes. All these advantages make this method valuable 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.2023.06.002.

References

1 P. Schneider and G. Schneider, *Angew. Chem., Int. Ed*., 2017, **56**, 7971.
2 *Multicomponent Reactions: Synthesis of Bioactive Heterocycles*, eds. K. L. Ameta and A. A. Dandia, CRS Press, Boca Raton, FL, 2017.
3 S. Katsamakas, A. G. Papadopoulos, M. G. Kouskoura and C. K. Markopoulou, *Future Med. Chem*., 2019, **11**, 2063.
4 *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, eds. L. L. Brunton, J. S. Lazo, K. L. Parker, I. Buxton and D. Blumenthal, 11th edn., McGraw-Hill, New York, 2006.
5 F. Grams, H. Brandstetter, S. D'Alò, D. Geppert, H. W. Krell, H. Leinert, V. Livi, E. Menta, A. Oliva and G. Zimmermann, *Biol. Chem*., 2001, **382**, 1277.

† *Compounds* **2a**–**j** *(typical procedure)*. A mixture of morpholinium 3-[(aryl)(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-6-methyl-2-oxo-2*H*-pyran-4-olate **1a**–**j** (1 mmol), NBS (0.21 g, 1.2 mmol) and AcONa (0.08 g, 1 mmol) was stirred in EtOH (4 ml) at room temperature for 1 h. After the reaction was complete, the formed solid was filtered off, and then rinsed with an ice-cold EtOH/water solution (1 : 1, 3 ml), and dried under reduced pressure to afford pure 3-aryl-1′,3′,6-trimethyl-2′*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine]-2′,4,4′,6′(1′*H*,3′*H*)-tetrone **2a**–**j**. For characteristics of the products, see Online Supplementary Materials.

6 G. P. McGlacken and I. J. S. Fairlamb, *Nat. Prod. Rep*., 2005, **22**, 369.
7 J. V. N. Vara Prasad, A. Pavlovsky, K. S. Para, E. L. Ellsworth, P. J. Tummino, C. Nouhan and D. Ferguson, *Bioorg. Med. Chem. Lett*., 1996, **6**, 1133.
8 Q.-Y. Lan, Q.-L. Liu, J. Cai and A.-W. Liu, *Int. J. Clin. Exp. Pathol*., 2015, **8**, 155.
9 P.-H. Yin, X. Liu, Y.-Y. Qiu, J.-F. Cai, J.-M. Qin, H.-R. Zhu and Q. Li, *Asian. Pac. J. Cancer Prev*., 2012, **13**, 5339.
10 Y. Zheng, C. M. Tice and S. V. Singh, *Bioorg. Med. Chem. Lett*., 2014, **24**, 3673.
11 Y. Zheng and C. M. Tice, *Expert Opin. Drug Discov*., 2016, **11**, 831.
12 K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150.
13 E. M. Galati, M. T. Monforte, N. Miceli and E. Ranerill, *Farmaco*, 2001, **56**, 459.
14 S.-H. Kim, A. T. Pudzianowski, K. J. Leavitt, J. Barbosa, P. A. McDonnell, W. J. Metzler, B. M. Rankin, R. Liu, W. Vaccaro and W. Pitts, *Bioorg. Med. Chem. Lett*., 2005, **15**, 1101.
15 W. Fraser, C. J. Suckling and H. C. S. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3137.
16 M. N. Elinson, A. N. Vereshchagin and F. V. Ryzhkov, *Chem. Rec*., 2016, **16**, 1950.
17 M. N. Elinson, E. O. Dorofeeva, A. N. Vereshchagin and G. I. Nikishin, *Russ. Chem. Rev*., 2015, **84**, 485.
18 A. N. Vereshchagin, M. N. Elinson, E. O. Dorofeeva, T. A. Zaimovskaya, N. O. Stepanov, S. V. Gorbunov, P. A. Belyakov and G. I. Nikishin, *Tetrahedron*, 2012, **68**, 1198.
19 B. Wang and H. N. C. Wong, *Bull. Chem. Soc. Jpn*., 2018, **91**, 710.
20 M. N. Elinson, S. K. Feducovich, N. O. Stepanov, A. N. Vereshchagin and G. I. Nikishin, *Tetrahedron*, 2008, **64**, 708.
21 A. N. Vereshchagin, M. N. Elinson, N. O. Stepanov and G. I. Nikishin, *Mendeleev Commun*., 2009, **19**, 324.
22 M. N. Elinson, A. N. Vereshchagin, N. O. Stepanov, A. I. Ilovaisky, A. Y. Vorontsov and G. I. Nikishin, *Tetrahedron*, 2009, **65**, 6057.
23 A. N. Vereshchagin, M. N. Elinson, T. A. Zaimovskaya and G. I. Nikishin, *Tetrahedron*, 2013, **69**, 1945.
24 M. J. Mphahlele, *Molecules*, 2009, **14**, 4814.
25 T. Rosen, in *Comprehensive Organic Synthesis*, eds. B. M. Trost, I. Flemingand and C. H. Heathcock, Pergamon, Oxford, 1991, vol. 2, pp. 395–408.
26 T. Cleary, T. Rawalpally, N. Kennedy and A. Chaves, *Tetrahedron Lett*., 2010, **51**, 1533.
27 M. N. Elinson, A. N. Vereshchagin, S. K. Feducovich, T. A. Zaimovskaya, Z. A. Starikova, P. A. Belyakov and G. I. Nikishin, *Tetrahedron Lett*., 2007, **48**, 6614.
28 I. Saikia, A. J. Borah and P. Phukan, *Chem. Rev*., 2016, **116**, 6837.
29 J. Y. Wang, P. Zhou, G. Li, W. J. Hao, S. J. Tu and B. Jiang, *Org. Lett*., 2017, **19**, 6682.
30 Y. Wei, S. Lin, H. Xue, F. Liang and B. Zhao, *Org. Lett*., 2012, **14**, 712.
31 C. Huang, Y. Zeng, H. Cheng, A. Hu, L. Liu, Y. Xiao and J. Zhang, *Org. Lett*., 2017, **19**, 4968.
32 M. Chakrabarty, T. Kundu, S. Arima and Y. Harigaya, *Tetrahedron Lett*., 2005, **46**, 2865.
33 Y. E. Ryzhkova, M. N. Elinson, A. N. Vereshchagin, K. A. Karpenko, F. V. Ryzhkov, I. E. Ushakov and M. P. Egorov, *Chemistry*, 2022, **4**, 615.
34 M. N. Elinson, A. N. Vereshchagin, N. O. Stepanov, P. A. Belyakov and G. I. Nikishin, *Tetrahedron Lett.*, 2010, **51**, 6598.

Received: 28th February 2023; Com. 23/7112