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Tandem Knoevenagel–Michael reaction with oxidative cyclization in the synthesis of spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine] scaffold

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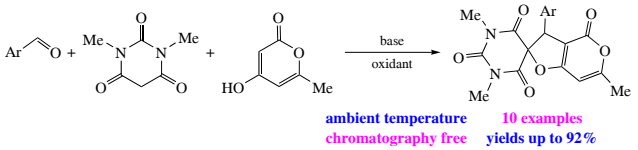
The new multicomponent one-pot tandem Knoevenagel–Michael reaction between aromatic aldehydes, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one proceeds in alcohols at ambient temperature to selectively afford new substituted unsymmetrical spiro-[furo[3,2-*c*]pyran-2,5′-pyrimidine] derivatives with two different heterocyclic rings. The procedure involves available non-expensive reactants, mild and convenient conditions, does not require chromatographic isolation and provides excellent yields. The compounds thus obtained are promising for different biomedical applications.



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Multicomponent reactions (MCRs) are now one of the main synthetic routes in a diversity-oriented way to maximum structural complexity in minimum steps.[1–3] In tandem processes, several stages follow one after another, and the subsequent stage is dependent on the type of new functional groups formed in the previous one.[4] This methodology has many advantages and has been developing successfully in the last two decades.[5] Tandem Knoevenagel–Michael reaction is also known in organic chemistry,[6] and until now, investigations in this area are in progress.[7,8]

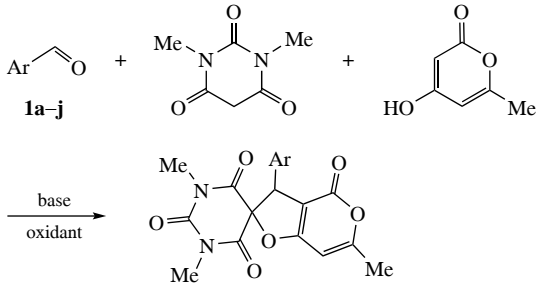
The use of privileged structures (scaffolds) is a rapidly developing area in medicinal chemistry. These structures are the classes of molecules capable of binding to multiple receptors with high affinity. The use of these definitions assists the medicinal chemist in discovering biologically active compounds with a broad range of therapeutic activities.[9] Barbiturates (pyrimidine-2,4,6-trione derivatives) represent a privileged medicinal scaffold[10] in different central nervous system drugs, sedatives, anticonvulsants, and anaesthetic agents.[11] Nowadays, a renewed interest to them arose because pyrimidinetrione template is an efficient zinc-chelating moiety and, thus, such derivatives demonstrate high selectivity toward matrix metalloproteinases responsible for cancer progression.[12] On the other hand, among different *O*-containing heterocycles 2*H*-pyran-2-ones are highly abundant in bacteria, microbial, plant, insect, and animal systems and take part in many types of biological processes.[13] Derivatives of 4-hydroxy-2*H*-pyran-2-ones exhibit anti-HIV[14] and anticancer[15] properties.

Spirocycles have been employed as privileged structures in drug discovery[16] since they have a reasonable balance between conformational rigidity and flexibility, which could lead to finding bioactive hits.[17] Barbiturate-containing spirocycles are a family of chemical entities with a wide range of biological activities and important medical applications.[18] Thus, spiro barbiturates have been established to exhibit neuropharmacological effects.[19] Recently, 1-phenyl-5,7-diazaspiro[2.5]octane-4,6,8-trione was identified as a tumor necrosis factor-alpha (TNF-α)-converting enzyme and matrix metalloproteinase inhibitor, suggesting that it could be used to treat a variety of inflammatory, infectious, and immunological diseases.[20]

Earlier,[21] we have realized multicomponent electrocatalytic approach to unsymmetrical spiro[furo[3,2-*c*]pyran-2,5′-pyrimidines] in an undivided cell in the presence of sodium halides with 70–85% yields. We have also accomplished spirocyclization of morpholinium 3-[(aryl)(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-6-methyl-2-oxo-2*H*-pyran-4-olates by the action of AcONa/NBS system in ethanol at room temperature with the formation of similar derivatives in 90–95% yields.[22] Considering our experience in tandem and multicomponent reactions with the formation of complex heterocyclic compounds[23,24] and their biomedical applications, we intended to design a more convenient access to spiro-[furo[3,2-*c*]pyran-2,5′-pyrimidine] scaffold.

This research is devoted to the selective and efficient three-component assembling of aromatic aldehydes **1a**–**j**, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one into spiro[furo[3,2-*c*]pyran-2,5′-pyrimidines] **2a**–**j** in alcohol under the action of base–oxidant systems (Scheme 1). To optimize the conditions, benzaldehyde **1a** was tested as the model substrate which was converted into 1′,3′,6-trimethyl-3-phenyl-2′*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine]-2′,4,4′,6′(1′*H*,3′*H*)-tetraone **2a** (Table 1).

Earlier, we used base–molecular halogen system to carry out one-pot transformation of alkylidenemalononitriles and malononitrile into substituted 1,1,2,2-tetracyanocyclopropanes[25] as well



1a–j **2a–j**

a Ar = Ph (91%)
b Ar = 2-MeC_6H_4 (92%)
c Ar = 4-MeC_6H_4 (90%)
d Ar = 3-$MeOC_6H_4$ (88%)
e Ar = 2-FC_6H_4 (86%)
f Ar = 4-FC_6H_4 (85%)
g Ar = 2-BrC_6H_4 (83%)
h Ar = 4-BrC_6H_4 (85%)
i Ar = 2-ClC_6H_4 (84%)
j Ar = 3-ClC_6H_4 (86%)

Scheme 1

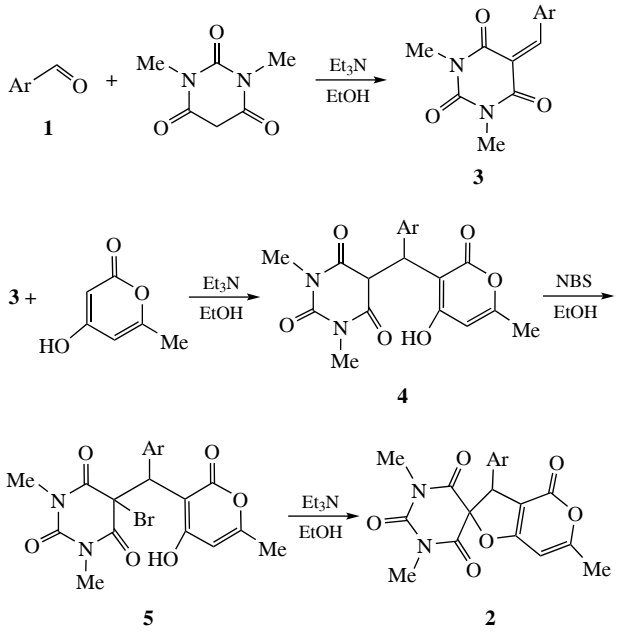
Table 1 Optimization of the one-pot synthesis of spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine] **2a**.[a]

Entry	Method	Base	Oxidant	Solvent	*t*/min	Yield of **2a** (%)
1	A	KOH	Br_2	EtOH	30	35
2	A	KOH	I_2	EtOH	30	32
3	A	NaOH	Br_2	EtOH	30	39
4	A	NaOH	I_2	EtOH	30	35
5	A	NaOAc	Br_2	EtOH	30	46
6	A	NaOAc	I_2	EtOH	30	41
7	A	NaOAc	NBS	EtOH	30	65
8	A	Et_3N	Br_2	EtOH	30	56
9	A	Et_3N	NBS	EtOH	30	74
10	A	morpholine	NBS	EtOH	30	69
11	A	Et_3N	NBS	MeOH	30	67
12	A	Et_3N	NBS	Pr^iOH	30	64
13	B	Et_3N	NBS	EtOH	30 + 30	91
14	B	Et_3N	NBS	EtOH	30 + 60	88

[a] Benzaldehyde **1a** (2 mmol), *N*,*N*′-dimethylbarbituric acid (2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol), base (2 mmol) and oxidant (2.4 mmol) were stirred in a solvent (5 ml) at ambient temperature (30 min) [method A]. Benzaldehyde **1a** (2 mmol), *N*,*N*′-dimethylbarbituric acid (2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol), and base (2 mmol) were stirred in EtOH (5 ml) at ambient temperature for 30 min, then NBS (2.4 mmol) was added, and stirring was continued for another 30 min [method B].

as for the analogous one-pot reaction of carbonyl compounds and malononitrile.[26] Sodium acetate is an inexpensive, nontoxic and readily available base catalyst for many types of organic reactions. In this study, NaOAc was found to be a sufficiently good base in the base-NBS oxidant system (see Table 1, entry 7). Triethylamine, an N-type base, is catalytically efficient for the Knoevenagel condensation and Michael addition reactions at room temperature providing good to excellent yields of products.[27] In our work, Et_3N was found to be the best base in the base-NBS oxidant system (entries 9, 11–14). *N*-Bromosuccinimide (NBS) is an efficient, selective, and versatile reagent in organic chemistry[28] and usually more selective than molecular bromine.[28–30] In this research, it turned out to be the best oxidant for our purpose (entries 7, 9–14).

Under the conditions of method A with the simultaneous addition of Et_3N and NBS, the best result was achieved with EtOH as solvent when product **2a** was obtained in a 74% yield (see Table 1, entry 9). The next improvement has been implemented in method B, when NBS was added 30 min after introducing Et_3N. With method B, product **2a** was obtained in the best 91% yield (entry 13).



Scheme 2

Under the optimal conditions thus found [EtOH, ambient temperature, Et_3N (30 min), NBS (30 min), (method B)], compounds **2a–j** were obtained in 83–92% yields from the corresponding benzaldehydes **1a–j** (see Scheme 1). In all these cases, after the end of the reaction the mixture was filtered, the solid on filter was rinsed with minimum ice-cold ethanol/water solution (1 : 1), and dried under reduced pressure. Compounds **2a–c** are known,[21,22] while the structure of new compounds **2d–j** was confirmed by ^1H, ^{13}C NMR, and IR spectroscopy, as well as mass spectrometry data.

Taking into consideration the above result and the data for the mechanisms of the multicomponent transformations of carbonyl compounds and CH acids,[31] the mechanism for the multicomponent transformation of aldehydes **1**, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one into spiro derivatives **2** may be proposed (Scheme 2). In the first stage, Et_3N-catalyzed reaction of aldehyde **1** and *N*,*N*′-dimethylbarbituric acid results in the Knoevenagel adduct **3** formation. Further Michael addition of 4-hydroxy-6-methyl-2*H*-pyran-2-one to the activated double bond of the Knoevenagel adduct **3** leads to the Michael adduct **4**. Bromination of the latter with NBS affords bromo intermediate **5** whose final base-assisted cyclization leads to the final spiro[furo[3,2-*c*]pyran-2,5′-pyrimidine] **2**.

In conclusion, the new type of chemical one-pot Knoevenagel–Michael reaction followed by NBS-induced cyclization was found, namely, the straightforward multicomponent assembly of aldehydes **1**, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one into substituted spiro[furo[3,2-*c*]-pyran-2,5′-pyrimidines] **2** in 83–92% yields. This one-pot procedure is very efficient and convenient, the reaction occurs under mild conditions and the products do not demand chromatographic purification. The compounds thus obtained seem promising for different biomedical applications since they contain privileged moieties in their structures, and can also find application 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: 10.71267/mencom.7660.

References

1 S. G. Zlotin, K. S. Egorova, V. P. Ananikov, A. A. Akulov, M. V. Varaksin, O. N. Chupakhin, V. N. Charushin, K. P. Bryliakov, A. D. Averin, I. P. Beletskaya, E. L. Dolengovski, Yu. H. Budnikova, O. G. Sinyashin, Z. N. Gafurov, A. O. Kantyukov, D. G. Yakhvarov, A. V. Aksenov, M. N. Elinson, V. G. Nenajdenko, A. M. Chibiryaev, N. S. Nesterov, E. A. Kozlova, O. N. Martyanov, I. A. Balova, V. N. Sorokoumov, D. A. Guk, E. K. Beloglazkina, D. A. Lemenovskii, I. Yu. Chukicheva, L. L. Frolova, E. S. Izmest'ev, I. A. Dvornikova, A. V. Popov, A. V. Kutchin, D. M. Borisova, A. A. Kalinina, A. M. Muzafarov, I. V. Kuchurov, A. L. Maximov and A. V. Zolotukhina, *Russ. Chem. Rev*., 2023, **92**, RCR5104; https://doi.org/10.59761/RCR5104.

2 M. N. Elinson, Yu. E. Ryzhkova and F. V. Ryzhkov, *Russ. Chem. Rev*., 2021, **90**, 94; https://doi.org/10.1070/rcr4972.

3 S. Zhi, X. Ma and W. Zhang, *Bioorg. Med. Chem*., 2019, **17**, 7632; https://doi.org/10.1039/C9OB00772E.

4 T. L. Ho, *Tandem Organic Reactions*, John Wiley & Sons, New York, 1992; https://doi.org/10.1002/recl.19931120912.

5 Y. Wang and H. Zhao, *Catalysts*, 2016, **6**, 194; https://doi.org/10.3390/catal6120194.

6 A. Behr, A. J. Vorholt, K. A. Ostrowski and T. Seidensticker, *Green Chem*., 2014, **16**, 982; https://doi.org/10.1039/C3GC41960F.

7 S. N. Jadhav, S. P. Patil, D. P. Sahoo, D. Rath, K. Parida and C. V. Rode, *Catal. Lett*., 2020, **150**, 2331; https://doi.org/10.1007/s10562-019-03089-8.

8 M. Liu, C.-F. Liu, J. Zhang, Y.-J. Xu and L. Dong, *Org. Chem. Front*., 2019, **6**, 664; https://doi.org/10.1039/C8QO01378K.

9 K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc*., 2000, **122**, 9939; https://doi.org/10.1021/ja002033k.

10 S. Katsamakas, A. G. Papadopoulos, M. G. Kouskoura, C. K. Markopoulou and D Hadjipavlou-Litina, *Future Med. Chem*., 2019, **11**, 2063; https://doi.org/10.4155/fmc-2018-0541.

11 *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, 11th edn., eds. L. L. Brunton, J. S. Lazo and K. L. Parker, McGraw Hill, New York, 2006; https://farmasi.unimman.ac.id/wp-content/uploads/2022/07/Goodman-Gilmans-The-Pharmacological-Basis-of-Therapeutics-11th-Edition-2006.pdf.

12 F. Grams, H. Brandstetter, S. D'Alo, D. Geppert, H. W. Krell, H. Leinert, V. Livi, E. Menta, A. Oliva and G. Zimmermann, *Biol. Chem.*, 2001, **382**, 1277; https://doi.org/10.1515/BC.2001.159.

13 G. P. McGlacken and I. J. S. Fairlamb, *Nat. Prod. Rep*., 2005, **22**, 369; https://doi.org/10.1039/B416651P.

14 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; https://doi.org/10.1016/0960-894X(96)00185-0.

15 Q.-Y. Lan, Q.-L. Liu, J. Cai and A.-W. Liu, *Int. J. Clin. Exp. Pathol*., 2015, **8**, 155; https://pmc.ncbi.nlm.nih.gov/articles/PMC4348880/pdf/ijcep0008-0155.pdf.

16 Y. Zheng, C. M. Tice and S. V. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673; https://doi.org/10.1016/j.bmcl.2014.06.081.

17 G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe and J. Bajorath, *Chem. – Eur. J*., 2017, **23**, 703; https://doi.org/10.1002/chem.201604714.

18 K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem*., 2021, **64**, 150; https://doi.org/10.1021/acs.jmedchem.0c01473.

19 E. M. Galati, M. T. Monforte, N. Miceli and E. Raneri, *Farmaco*, 2001, **56**, 459; https://doi.org/10.1016/S0014-827X(01)01062-X.

20 J. Duan, B. Jiang, L. Chen, Z. Lu, J. Barbosa and W. J. Pitts, *Patent WO 2003053941*, 2003.

21 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; https://doi.org/10.3390/chemistry4020044.

22 M. N. Elinson, A. N. Vereshchagin, Y. E. Ryzhkova, K. A. Karpenko, V. M. Kalashnikova and M. P. Egorov, *Mendeleev Commun*., 2023, **33**, 448; https://doi.org/10.1016/j.mencom.2023.06.002.

23 A. N. Vereshchagin, M. N. Elinson, F. V. Ryzhkov, R. F. Nasybullin, S. I. Bobrovsky, A. S. Goloveshkin and M. P. Egorov, *C. R. Chim*., 2015, **18**, 1344; https://doi.org/10.1016/j.crci.2015.02.005.

24 M. N. Elinson, M. G. Medvedev, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya and G. I. Nikishin, *Mendeleev Commun*., 2013, **23**, 94; https://doi.org/10.1016/j.mencom.2013.03.014.

25 A. N. Vereshchagin, M. N. Elinson, N. O. Stepanov and G. I. Nikishin, *Mendeleev Commun*., 2009, **19**, 324; https://doi.org/10.1016/j.mencom.2009.11.010.

26 M. N. Elinson, A. N. Vereshchagin, N. O. Stepanov, A. I. Ilovaisky, A. Y. Vorontsov and G. I. Nikishin, *Tetrahedron*, 2009, **65**, 6057; https://doi.org/10.1016/j.tet.2009.05.062.

27 A. R. Bhat, R. S. Selokar, J. S. Meshram and R. S. Dongre, *J. Mater. Environ. Sci*., 2014, **5**, 1653; https://www.jmaterenvironsci.com/Document/vol5/vol5_N5/202-JMES-954-2014-Bhat.pdf.

28 I. Saikia, A. J. Borah and P. Phukan, *Chem. Rev.*, 2016, **116**, 6837; https://doi.org/10.1021/acs.chemrev.5b00400.

29 J. Y. Wang, P. Zhou, G. Li, W. J. Hao, S. J. Tu and B. Jiang, *Org. Lett.*, 2017, **19**, 6682; https://doi.org/10.1021/acs.orglett.7b03410.

30 Y. Wei, S. Lin, H Xue, F. Liang and B. Zhao, *Org. Lett*., 2012, **14**, 712; https://doi.org/10.1021/ol203183k.

31 M. N. Elinson, A. N. Vereshchagin and F. V. Ryzhkov, *Chem. Rec*., 2016, **16**, 1950; https://doi.org/10.1002/tcr.201600044.

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