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Non-catalytic thermal multicomponent assembling of isatin, cyclic CH-acids and malononitrile: an efficient approach to spirooxindole scaffold

Michail N. Elinson,*[a] Alexey I. Ilovaisky,[a] Valentina M. Merkulova,[a] Tatiana A. Zaimovskaya[b] and Gennady I. Nikishin[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] *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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Thermal non-catalytic reaction of isatin, cyclic CH-acids and malononitrile in water or alcohols affords substituted spirooxindoles in 90–97% yields.

In recent years the concept of 'privileged medicinal structures or scaffolds'[1,†] has emerged as one of the guiding principles of drug discovery process. These privileged scaffolds commonly consist of rigid hetero ring system that assigns well-defined orientation of appended functionalities for target recognition.[2] The indole scaffold represents an important structural subunit for the discovery of new drug candidates.[3] Isatin (1*H*-indole-2,3-dione) and its derivatives have also sufficient application in medicinal chemistry.[4]

The heterocyclic spirooxindole scaffold is widely distributed in a number of pharmaceuticals and natural products[5–7] and is regarded as an attractive synthetic target.[8]

The general approach to formation of spirooxindoles utilizes catalytic multicomponent procedures with using large amounts (20–100%) of diverse catalysts.[9–14] The procedure is also known in the electrocatalytic variant.[15–17] However, prolonged reaction time, moderate yields and complexity of isolation or necessity to use sufficient quantities of catalyst are the main drawbacks of the known methods. Thus, the search for advanced procedures for the synthesis of spirooxindoles such as fast and convenient non-catalytic MCR methodology seems topical.

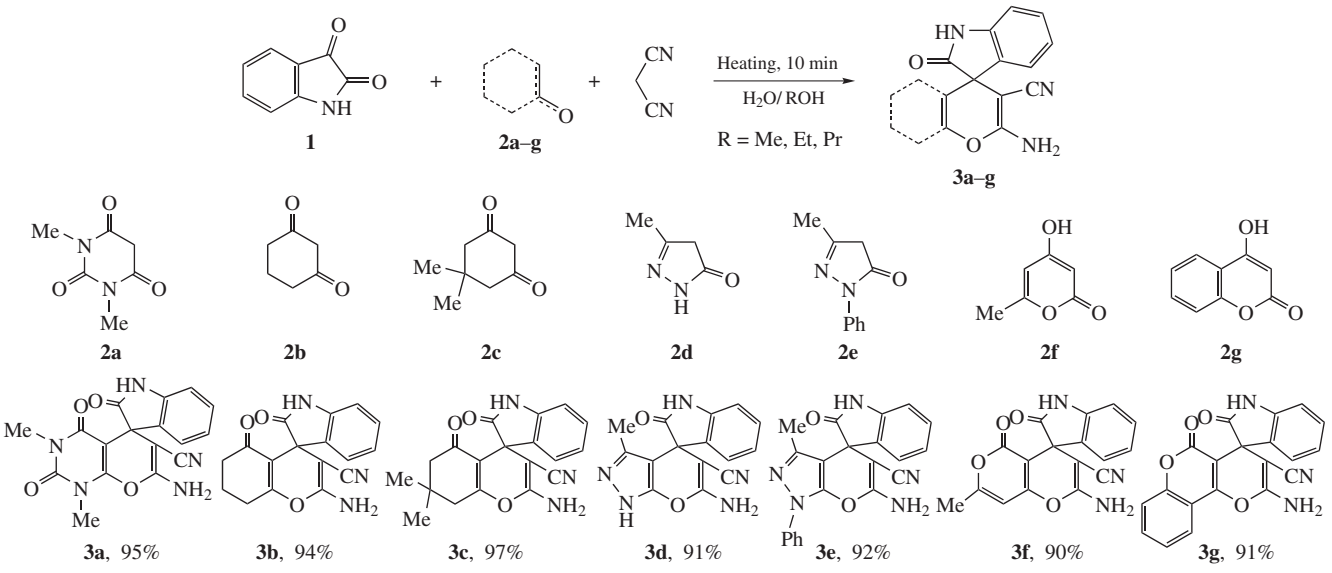
Table 1 One-pot transformation of isatin **1**, *N*,*N*′-dimethylbarbituric acid **2a** and malononitrile into 7′-amino-1′,3′-dimethyl-2,2′,4′-trioxo-1,1′,2,2′,3′,4′-hexahydrospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile **3a**.[a]

Entry	Solvent	*T*/°C	Yield of **3a** (%)[b]
1	H_2O	60	81
2	H_2O	80	90
3	MeOH	64	85
4	EtOH	78	91
6	PrOH	97	95

[a] **1** (5 mmol), **2a** (5 mmol), malononitrile (5 mmol), 10 min. [b] Isolated yield.

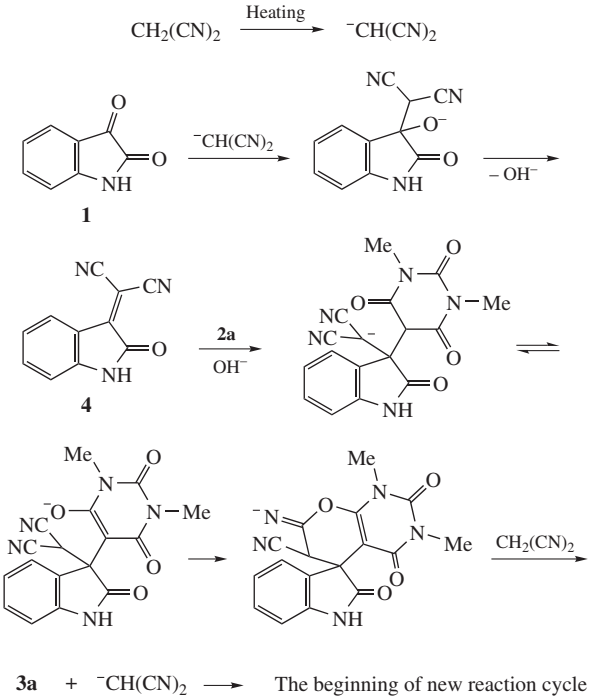
Recently we have developed catalytic 'on water' Knoevenagel condensation of isatins with malononitrile.[18] In the present study, we wish to report our results on assembling of isatin, cyclic CH-acids and malononitrile into substituted spirooxindoles under non-catalytic conditions (Scheme 1, Table 1).

When the reaction of isatin **1**, *N*,*N*′-dimethylbarbituric acid **2a** and malononitrile was performed under basic conditions,[18] spirooxindole **3a** was obtained in 55% yield (NMR data) along



Scheme 1

† The term 'privileged scaffolds or structures' was originally introduced by Merck researchers in their work on benzodiazepins (see ref. 1).



Scheme 2

with the Knoevenagel adduct of isatin with malononitrile – compound **4** (31% yield, Scheme 2).

The solvent-free performance of this reaction at 60 °C resulted in the formation of spirooxindole **3a** in 63% yield (NMR data), whereas the addition of small quantity of water led to the yield rise up to 81%. Raising the temperature to 80 °C resulted in increasing this yield to 90%. The high yields of **3a** were also achieved when the reaction was carried out in methanol, ethanol or propanol (entries 3–6, Table 1), however, the highest yield (95%) of the product was reached in propanol at 97 °C within 10 min.

Under the optimal conditions thus found (propanol as a solvent, 97 °C, reaction time of 10 min) isatin **1**, cyclic CH-acids **2a–g** and malononitrile were transformed into corresponding spirooxindoles **3a–g** isolated in 90–97% yields (Scheme 1).‡

Taking into consideration the above results and the data on non-catalytic 'on water' Knoevenagel condensation of isatins with malononitrile[18] the following mechanism for the transformation in study is proposed (see Scheme 2, shown for the case of **2a** as cyclic CH-acid). At the initiation step of the catalytic circle, the thermal deprotonation of malononitrile leads to the generation of malononitrile anion (*cf.* refs. 19, 20). Then Knoevenagel condensation of malononitrile anion with isatin **1** takes place in the solution with elimination of hydroxide anion and formation of the Knoevenagel adduct **4**.[21] The subsequent hydroxide-promoted Michael addition of barbituric acid **2a** to electron deficient Knoevenagel adduct **4** followed by intramolecular cyclization results in spirooxindole **3a** with regeneration of malononitrile anion at the last step, which continues the catalytic chain process by the interaction with the next molecule of isatin **1**. Thus, the generation of even single malononitrile anion is theoretically sufficient for the total conversion of equimolar quantities of isatins, cyclic CH-acids and malononitrile into the corresponding spirooxindoles **3a–g**.

In conclusion, the simple non-catalytic system can produce, under neutral conditions, a fast (10 min) and selective multicomponent transformation of isatin, cyclic CH-acids and malononitrile into spirooxindoles **3a–g** in 90–97% yields. This novel thermal chain process opens fast and efficient way to spirooxindole derivatives – the promising compounds for the different biomedical applications. The procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes.

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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.2012.05.010.

References

1 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, F. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235.
2 J. Poupaert, P. Carato and E. Colacino, *Curr. Med. Chem.*, 2005, **12**, 877.
3 F. R. De Sá Alves, C. A. M. Fraga and E. J. Barreiro, *Mini Rev. Med. Chem*., 2009, **9**, 782.
4 (*a*) J. F. M. Da Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc*., 2001, **12**, 273; (*b*) S. N. Pandeya, S. Smitha, M. Jyoti and S. K. Sridhar, *Acta Pharm*., 2005, **55**, 27; (*c*) D. Shiram, T. R. Bal and P. Yogeeswari, *J. Pharm. Pharm. Sci.*, 2005, **8**, 565; (*d*) N. Karali, A. Gursoi, F. Kandemirli, N. Shvets, F. B. Kaynak, S. Ozbey, V. Kovalishyn and A. Dimoglo, *Bioorg. Med. Chem.*, 2007, **15**, 5888.
5 R. M. Williams and R. J. Cox, *Acc. Chem. Res*., 2003, **36**, 127.
6 C. B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **52**, 12651.
7 J. Leclercq, M. C. de Pauw-Gillet, R. Bassleer and L. Angenot, *J. Ethnopharmacol.*, 1986, **15**, 305.
8 P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel and E. M. Carreira, *Angew. Chem. Int. Ed.*, 1999, **38**, 3186.
9 A. A. Shestopalov, L. A. Rodinovskaya, A. M. Shestopalov and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 968 (*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 992).
10 S. Gao, C. H. Tsai, C. Tseng and C. F. Yao, *Tetrahedron*, 2008, **64**, 9143.
11 L. M. Wang, N. Jiao, J. Qiu, J. J. Yu, J. Q. Liu, F. L. Guo and Y. Liu, *Tetrahedron*, 2010, **66**, 339.
12 G. Shanthi, G. Subbulakshmi and P. T. Perumal, *Tetrahedron*, 2007, **63**, 2057.
13 L. A. Shemchuk, V. P. Chernykh and R. G. Red'kin, *Zh. Org. Khim.*, 2008, **44**, 1816 (*Russ. J. Org. Chem*., 2008, **44**, 1789).
14 G. S. Hari and Y. R. Lee, *Synthesis*, 2010, 453.
15 M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, N. O. Stepanov, D. V. Demchuk, P. A. Belyakov and G. I. Nikishin, *Electrochim. Acta*, 2008, **53**, 8346.
16 M. N. Elinson, A. I. Ilovaisky, A. S. Dorofeev, V. M. Merkulova, N. O. Stepanov, F. M. Miloserdov, Yu. N. Ogibin and G. I. Nikishin, *Tetrahedron*, 2007, **63**, 10543.
17 M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov and G. I. Nikishin, *Mol. Diversity*, 2009, **13**, 47.
18 D. V. Demchuk, M. N. Elinson and G. I. Nikishin, *Mendeleev Commun.*, 2011, **21**, 224.
19 R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc*., 1953, **75**, 2439.
20 R. P. Mariella and A. J. Roth, *J. Org. Chem.*, 1957, **22**, 1130.
21 S. Patai and Y. Israeli, *J. Chem. Soc.*, 1960, 2025.

‡ *General procedure*. A mixture of isatin **1** (5 mmol, 0.74 g), cyclic CH-acid **2** (5 mmol), malononitrile (5 mmol, 0.33 g) and *n*-propanol (3 ml) was stirred under reflux for 10 min. Then the reaction mixture was cooled and filtered to isolate the solid product **3**, which was twice rinsed with ethanol (2×5 ml), and dried under reduced pressure.

For characteristics of compounds **3a–g**, see Online Supplementary Materials.

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