



Mendeleev Communications

## 'On water' Knoevenagel condensation of isatins with malononitrile

## Dmitry V. Demchuk, Michail N. Elinson\* and Gennady I. Nikishin

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

DOI: 10.1016/j.mencom.2011.07.018

Grinding of isatins with malononitrile in the presence of 1–5 equiv. of water for 15 min at room temperature affords the corresponding (2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)malononitriles, the Knoevenagel condensation products, in 89–99% yields.

Knoevenagel condensation is a nucleophilic addition of active hydrogen compound to carbonyl group followed by dehydration in which molecule of water is eliminated.<sup>1–3</sup> The reaction is catalyzed by various amines, ammonium salts or Lewis acids<sup>3–11</sup> and can be effected by microwave irradiation in the absence of the solvent.<sup>12–15</sup> Particularly, in recent years, reactions under solvent-free conditions have continuously attracted the attention of the researchers due to significant simplification of the procedure.

Condensation of aromatic aldehydes with malononitrile could not been achieved under solvent-free conditions at room temperature,<sup>16</sup> however, it was accomplished as melt reaction at 150 °C in 1 h.<sup>16</sup> An improved procedure for solvent-free condensation of aromatic aldehydes with malononitrile by 45 min grinding was reported.<sup>17</sup> The yields in the case of liquid aromatic aldehydes were 80–95%, except for benzaldehyde (only 68% of condensation product) because this aldehyde is volatilized during the grinding.<sup>13</sup> Recently an effective method was reported for the solvent-free condensation of benzaldehyde with malononitrile in 10 min with the mechanochemical mixing in the presence of MgO as the catalyst.<sup>18</sup>

The indole scaffold including isatin (1*H*-indole-2,3-dione) represents the important structural subunit for the discovery of new drug candidates.<sup>19</sup> Isatin 3-positioned carbonyl group is known to be active in various condensation reactions.

Here, we report our results on the solvent-free condensation of isatins with malononitrile under grinding conditions (Scheme 1, Table 1).<sup> $\dagger$ </sup>



<sup>&</sup>lt;sup>†</sup> *General procedure*. A mixture of isatine (2 mmol), malononitrile (145 mg, 2.2 mmol) and water (36–180 mg, 2–10 mmol) (Table 1) was mixed thoroughly in a mortar with pestle followed by grinding for 15 min. The resultant mixture was air dried to cause crystallization of the product. In some cases analytical samples of the product were additionally crystallized from ethanol.

For characteristics of (2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)malononitriles **2a–f**, see Online Supplementary Materials.

Table 1 Solvent-free and 'on water' condensation of isatins 1a-f with malononitrile.<sup>*a*</sup>

Isatin	Equiv. H <sub>2</sub> O	Product	Yield $(\%)^b$
1a	_	2a	75
1a	1	2a	81
1a	3	2a	99
1b	1	2b	99
1c	1	2c	99
1d	1	2d	99
1e	1	2e	81
1e	3	2e	85
1e	5	2e	93
1f	1	2f	78
1f	3	2f	89
1f	5	<b>2f</b>	96

<sup>*a*</sup>**1a** (2 mmol), malononitrile (2 mmol), 20 °C, grinding 15 min. <sup>*b*</sup>Isolated yields.

First, to evaluate the synthetic potential and to optimize the procedure proposed, the condensation of isatin **1a** with malononitrile leading to the product **2a** was studied (Table 1).

In fact, grinding of 2 mmol isatin **1a** with 2 mmol malonitrile for 15 min resulted in formation of **2a** in 75% yield. Surprisingly, the yield of **2a** in this procedure was raised to 99% by preliminary adding 3 equiv. of water to the reaction mixture. Under similar conditions the other substituted isatins **1b–f** were also efficiently converted into the corresponding adducts **2b–f** in 15 min in 89–99% yields.

The Knoevenagel condensation is strongly solvent-dependent. The first step (aldol addition) is facilitated in the solvents with the high polarity and the second step (1,2-elimination) is inhibited by protic solvents.<sup>2,3</sup> Our experiments indicate that grinding promotes the elimination step. To our knowledge, this is the first example of the Knoevenagel condensation between two solid compounds promoted by grinding at room temperature in the absence of solvents and any catalyst.

Note that 1–3 equiv. water additive caused raising the yield of the condensation product between **1a** and malononitrile from 75 to 99%. In the case of isatins bearing electron-withdrawing substituents **1e,f** the best results were obtained with adding 5 equiv. of water. Meanwhile, for isatins **1b–d** with electron-donating substituents, 1 equiv. of water was sufficient to reach the yields of 99%.

Isatins **1a–f** are insoluble in water. Being grinded, a mixture of isatin **1**, malononitrile and water form two phase solid–liquid system. The solid phase consists of isatin **1** and partly malononitrile, and liquid phase is the solution of malononitrile in water. Then, reaction of the water solution of malononitrile with solid isatins **1a–f** is activated by grinding in the same manner as in the case of liquid aldehydes.<sup>17</sup>

Water plays an essential role in life processes, however, its use as a solvent in organic synthesis has been limited. The role of water to accelerate organic reaction was known earlier.<sup>20</sup> Recently it was shown that certain uni- and bimolecular reactions are greatly accelerated when carried out in vigorously stirred aqueous suspensions.<sup>21</sup> The experiments were performed with one or two liquid, water-insoluble reactants or, occasionally, a mixture of one liquid and one solid. Although detailed kinetic experiments were not performed, the yields of pure products after varying reaction times convincingly demonstrate that the rates are higher than those under solvent-free ('neat') or homogeneous conditions.<sup>21</sup>

Recently the special term 'on water' reactions was introduced,<sup>21–23</sup> implying their carrying out in water dispersion with an unusual rate acceleration compared to the same reaction in organic solvent or without solvent. This effect has been known for many years but in 2005 Sharpless and co-workers presented a systematic study of this phenomenon.<sup>21,22</sup>

Apparently, in the present study water should facilitate the aldol formation step as solvent, while the second step (1,2-elimination) proceeds as 'on water' reaction, which is facilitated by grinding.

In summary, the herein discovered combination of 'on water' and grinding techniques brings us closer to the notion of green chemistry and 'ideal synthesis'.<sup>24</sup>

This work was supported by the Presidential Scholarship Program for State Support of Leading Science Schools of the Russian Federation (project no. 4945.2010.3).

## **Online Supplementary Materials**

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.07.018.

## References

- 1 E. Knoevenagel, Chem. Ber., 1894, 27, 2345.
- 2 G. Jones, Organic Reactions, Wiley, New York, 1967, vol. 15, p. 204.

- 3 B. M. Trost, *Comprehensive Organic Synthesis*, Pergamon Press, Oxford, 1991, vol. 2, p. 341.
- 4 W. Lehnert, *Synthesis*, 1974, 667.
- 5 P. S. Rao and R. V. Venkataratnam, Tetrahedron Lett., 1991, 32, 5821.
- 6 D. Prajapati and J. S. Sandhu, Chem. Lett., 1992, 1945.
- 7 D. Prajapati and J. S. Sandhu, J. Chem. Soc., Perkin Trans. 1, 1993, 739.
- 8 I. A. Abdelhamid, Synlett., 2009, 625.
- 9 S.-L. Zhu, K. Zhao, X-M. Su and S-J Ji, Synth. Commun., 2009, 39, 1355.
- 10 I. A. Abdelhamid, M. H. Mohamed, A. M. Abdelmoneim and S. A. S. Ghozlan, *Tetrahedron*, 2009, 65, 10069.
- 11 H. Liu, G. Dou and D. Shi, J. Comb. Chem., 2010, 12, 292.
- 12 S. Abdallah-El Ayoubi, F. Texier-Boullet and J. Hamelin, Synthesis, 1994, 258.
- 13 D. Villemin, E. Diez-Barrra, A. Loupy and F. Langa, *Tetrahedron Lett.*, 1996, 37, 1113.
- 14 S. Y. Kim, P. S. Kwon and W. T. Kwon, Synth. Commun., 1997, 27, 533.
- 15 P. S. Kwon, S. Y. Kim and J. Kang, Synth. Commun., 1997, 27, 4091.
- 16 G. Kaupp, M. R. Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2003, 59, 3753.
- 17 Z. Ren, W. Cao and W. Tong, Synth. Commun., 2002, 32, 3475.
- 18 D. Kumar, V. B. Reddy, S. Sharad, U. Dube and S. Kapur, *Eur. J. Med. Chem.*, 2009, 44, 3805.
- 19 S. N. Pandeya, S. Smitha, M. Jyoti and S. K. Sridhar, Acta Pharm., 2005, 55, 27.
- 20 Organic Reactions in Water: Principles, Strategies and Applications, ed. N. M. Lindström, Blackwell, Oxford, 2007.
- 21 S. Narayan, J. Muldoon, M. J. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2005, 44, 3275.
- 22 J. E. Klijn and J. B. Engberts, Nature, 2005, 435, 746.
- 23 A. Chanda and V. V. Fokin, Chem. Rev., 2009, 109, 725.
- 24 P. A. Wender, S. T. Handy and D. L. Wright, *Chem. Ind. (London)*, 1997, 765.

Received: 24th December 2010; Com. 10/3650