Structure of the intermediate in the synthesis of 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

Nikolay Yu. Gorobets,* Yuriy V. Sedash, Svetlana V. Shishkina, Oleg V. Shishkin, Sergey A. Yermolayev, and Sergey M. Desenko

Department of Chemistry of Heterocyclic Compounds, State Scientific Institution 'Institute for Single Crystals' of National Academy of Science of Ukraine, Lenin Ave. 60, Kharkiv 61001, Ukraine
E-mail: gorobets@isc.kharkov.com

Abstract

4-(Dimethylamino)but-3-en-2-one **1a** reacted with malononitrile **2a** affording (2*E*,4*E*)-2-cyano-5-dimethylamino)hexa-2,4-dienamide **6aa** that was isolated as two isomers,1-s-*cis* and 1-s-*trans* **6aa** as confirmed by X-ray diffraction analysis. Acid-induced cyclization of 1-s-*cis* **6aa** gave the known 1,2-dihydro-6-methyl-2-oxopyridine-3-carbonitrile **3aa**, but not 1,2-dihydro-4-methyl-2-oxopyridine-3-carbonitrile **9aa** as reported previously. The mechanistic pathway of the 2-pyridone ring formation is discussed.

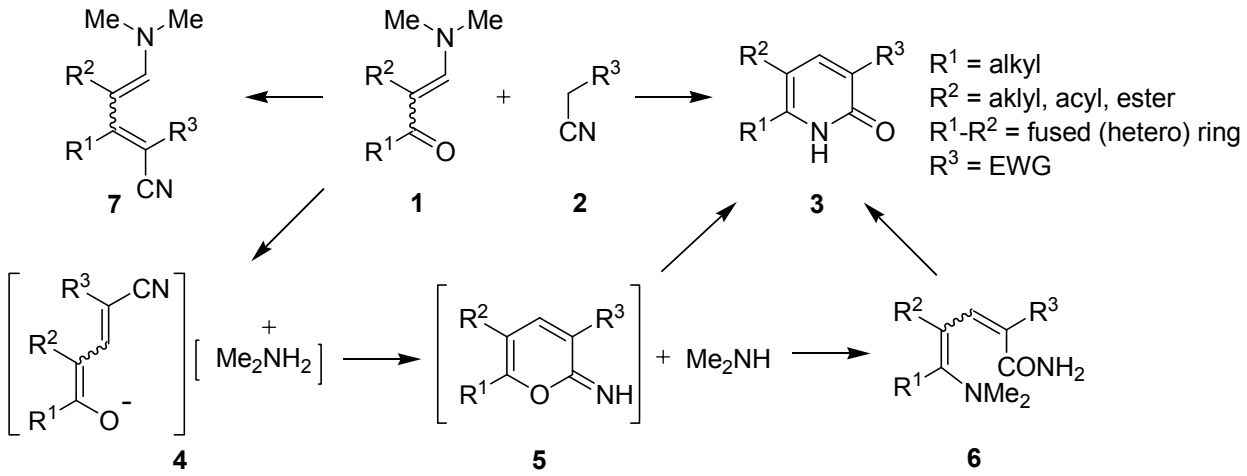
Keywords: 2-Pyridones, DMFDMA, conformers, Dimroth rearrangement, X-ray diffraction study, quantum-chemical calculations

Introduction

Various pharmaceutical applications of 2-pyridone derivatives **3** (Scheme 1) have attracted the attention of organic chemists with respect to their synthesis. One of the main synthetic strategies toward the synthesis of analogues of **3**[1–3] is the reaction of β-amino enones **1** with methylene active nitriles **2**.[4–8]

For the reaction of β-amino enones **1** with methylene active nitriles **2**, two kinds of reaction intermediates have been considered and isolated: dienolates of type **4**[5–14] and amide derivatives **6**[10] (Scheme 1). Supposedly, these products are formed by the initial conjugate addition of the α-methylene group of nitrile **2** to β-amino enone **1** followed by elimination of dimethylamine. The salt intermediate **4** may undergo 6-exo-dig cyclization to the postulated 2*H*-pyran-2-imine intermediate **5**,[10,15] which in turn, is transformed into 2-pyridone **3** via a Dimroth-like rearrangement[5–7] or via the amide **6**.[10] Apparently, intermediate **6** is formed upon addition of dimethylamine to iminopyrane **5** at 6-C followed by ring opening (reverse 6π electrocyclization).

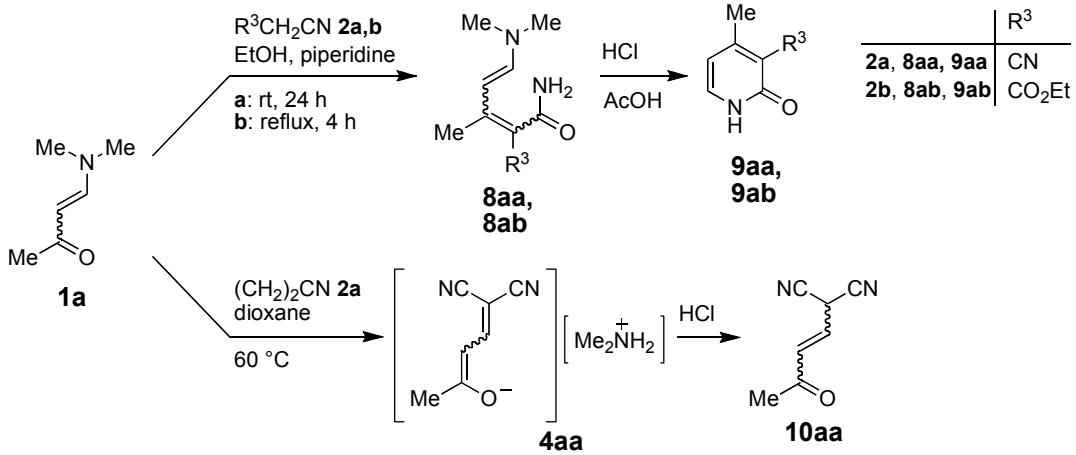
Finally, amide **6** undergoes ring closure (6π electrocyclization) followed by elimination of dimethylamine to yield the 2-pyridone derivative **3**.



Scheme 1

A different route has been also observed resulting from the condensation of the carbonyl function of enone **1** with the methylene group of nitriles **2**; nitriles **7** have been isolated as by-products or as low yield products (Scheme 1).[10]

In contrast, 4-dimethylamino-but-3-en-2-one **1a** has been reported[16] to react with malono-dinitrile **2a** or ethyl cyanoacetate **2b** to give amides **8aa** and **8ab**, respectively (Scheme 2). This is surprising, as it does not appear to be plausible that in the course of the condensation of the α-methylene group of nitriles **2a,b** with the carbonyl group of **1a** the cyano group is converted into the amide function of **8**. Amides **8** are isomers of amides **6** (R^1 = Me, R^2 = H; Scheme 1). The acid induced ring closure of amides **8** has been claimed to afford 4-methyl-2-oxo-1,2-dihydropyridine derivatives **9** (Scheme 2).[16]



Scheme 2

The same starting materials, β-aminoenone **1a** and malonodinitrile **2a** have been reported[17] to give the dienolate salt **4aa** (Scheme 2). Treatment of salt **4aa** with hydrochloric acid was claimed to form the open chain product 2-(3-oxobut-1-enyl)malononitrile **10aa**.[17]

In both publications,[16,17] structure elucidations were based on spectral data (IR,[16] ^{1}H NMR,[16,17] and ^{13}C NMR[16]) that did not allow one to distinguish between salt **4aa**,[17] amide **8aa**,[16] and its isomer **6aa** (R^1 = Me, R^2 = H, R^3 = CN). Likewise, the structures of the alleged final reaction products **9aa**[17] and **10aa**[16] have not been unambiguously proven. We assumed that the reaction of 4-(dimethylamino)but-3-en-2-one **1a** with nitrile **2a** may follow the same reaction path as outlined in Scheme 1; therefore, we decided to reinvestigate this reaction.[18]

Results and Discussion

The reaction of 4-(dimethylamino)but-3-en-2-one **1a** and malonodinitrile **2a** was carried out under the condition reported in the original work.[16] A red crystalline product was formed at room temperature after 24 h. X-ray analysis of the crude product revealed the structure of 1-s-*cis*-(2*E*,4*E*)-2-cyano-5-(dimethylamino)hexa-2,4-dienamide (1-s-*cis* **6aa**) (Figure 1). Recrystallization from acetic acid afforded the yellow conformer 1-s-*trans*-(2*E*,4*E*)-2-cyano-5-(dimethylamino)hexa-2,4-dienamide (1-s-*trans* **6aa**) as proven by X-ray analysis (Figure 1).

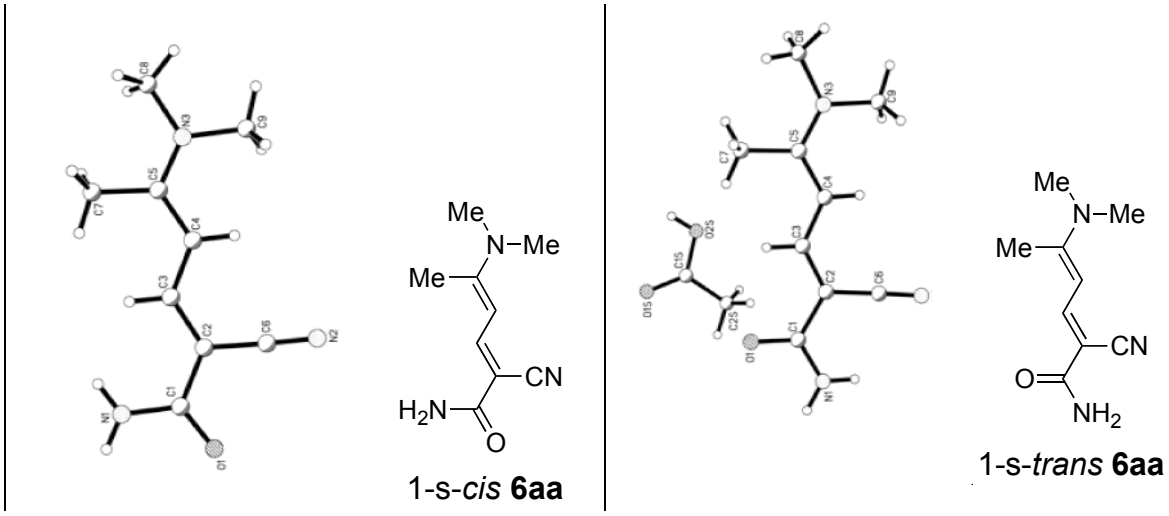
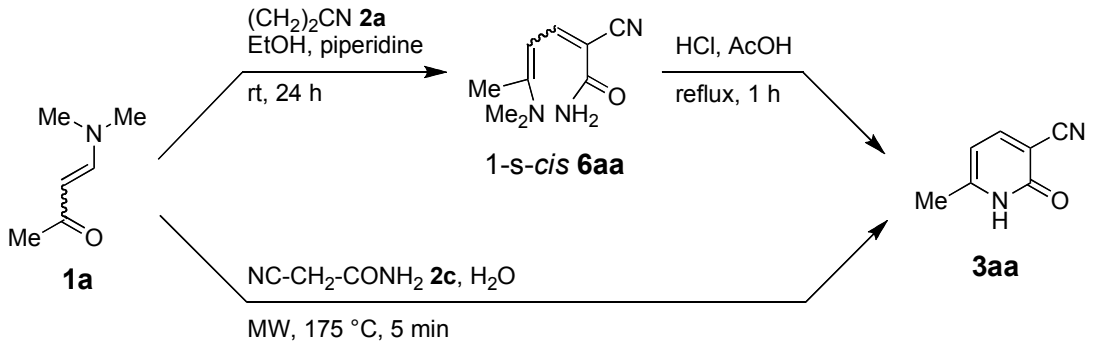


Figure 1. Single crystal X-ray structures of the conformational isomers 1-s-*cis*- and 1-s-*trans*-(2*E*,4*E*)-2-cyano-5-(dimethylamino)hexa-2,4-dienamide **6aa**.

^{1}H NMR data obtained from DMSO-d_6 solutions of both amides 1-s-*cis* and 1-s-*trans* **6aa** are identical except for the additional methyl group singlet of acetic acid in the ^{1}H NMR spectrum of the latter forming an crystalline solvate with acetic acid (ratio 1:1) as confirmed by X-ray analysis. The solvate 1-s-*trans* **6aa**·AcOH loses acetic acid upon drying at 100 °C.

Thus, the reaction of 4-(dimethylamino)but-3-en-2-one **1a** and malonodinitrile **2a** yielded 1-s-*cis*-(2*E*,4*E*)-2-cyano-5-(dimethylamino)hexa-2,4-dienamide (1-s-*cis* **6aa**, Scheme 3), but not its isomer **8aa**[16] or the salt **4aa**[17] (Scheme 2). Treatment of amide 1-s-*cis* **6aa** with hydrochloric acid induced cyclization and elimination of dimethylamine forming 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **3aa**. Contrary to previous reports,[16,17] neither 4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **9aa**[16] nor 2-(3-oxobut-1-enyl)malononitrile **10aa**[17] were formed.

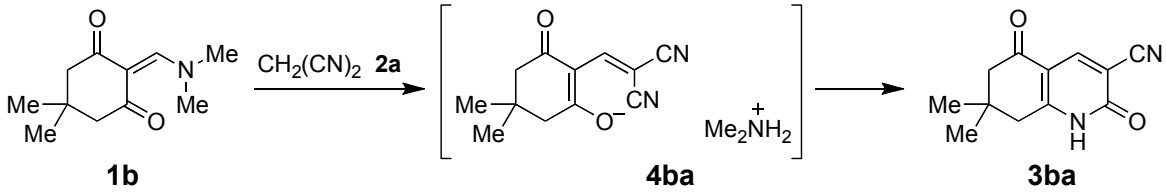
The structure of the known 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **3aa**[19–22] formed from amide 1-s-*cis* **6aa** was confirmed by matching ^{1}H NMR data[22] and by an alternative synthesis from β-amino enone **1a** and cyanoacetamide **2c** in water upon microwave irradiation.



Scheme 3

Only in the course of the reaction of open-chain enones **1**, the isolation of such amides **6** (cf. Scheme 1) has been reported;[10] ^{1}H NMR evidence indicated the presence of s-*cis* and s-*trans* amides **6**.[10]

There is only one report[17] about an open-chain enolate salt, i.e. **4aa** (cf. Scheme 2). The melting point and ^{1}H NMR data of this compound is very similar to those obtained for **6aa**. On the other hand, in the course of the reaction of cyclic dicarbonyl enamines like 2-[(dimethylamino)methylene]-5,5-dimethylcyclohexane-1,3-dione **1b** with malononitrile **2a** yielding 7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile **3ba** (Scheme 4),[5,6] the dienolate salt **4ba** can be isolated as a resonance stabilized[7] intermediate. So far, isolation of salts of type **4** has been reported only from substrates with fused carbo- or heterocyclic rings.[5–7,11–15]



Scheme 4

Structure analysis

The structure analyses of the rotational isomers 1-s-*cis* and 1s-*trans* **6aa** reveal that in the crystal phase both molecules are planar within 0.03 Å (1-s-*cis* **6aa**) and 0.05 Å (1s-*trans* **6aa**). Both 1-s-*cis* and 1s-*trans* **6aa** are sterically strained as evidenced by the very strong repulsion between atoms in both molecules (see Supplementary Information). The comparison of the bond lengths in the rotational isomers shows that all bonds are slightly longer in conformer 1s-*trans* **6aa** as compared with 1s-*cis* **6aa**. This indicates that the degree of conjugation depends on the orientation of the carbamide substituent.

In the crystal, 1-s-*cis* **6aa** forms centrosymmetric dimers due to the N(1)–H(1Nb)···O(1)' (-x, -y, 1-z) intermolecular hydrogen bond (H···O 2.01 Å, N–H···O 174°). The dimers are bonded by intermolecular hydrogen bond [N(1)–H(1Na)···N(2)' (x-1, y, z) (H···N 2.25 Å, N–H···N 158°)]. 1s-*trans* **6aa** crystallized together with acetic acid forming dimers via hydrogen bonds [O(2S)–H(2OS)···O(1)' (x-0.5, 0.5-y, z-0.5) (H···O 1.77 Å, O–H···O 170°) and N(1)–H(1Nb)···O(1S)' (x+0.5, 0.5-y, z+0.5) (H···O 2.05 Å, N–H···O 165°)]. These dimers are bonded by the N(1)–H(1Na)···O(1S)' (0.5-x, y-0.5, 1.5-z) (H···O 2.23 Å, N–H···O 139°) hydrogen bond. Both rotamers 1-s-*cis* and 1s-*trans* **6aa** form layers in the crystal. The distance between the layers is about 3.4 Å, assuming stacking interactions between the π-systems of the molecules.

Taking into account intermolecular interactions in the crystal phase leads to assume that the planar structure and significant polarization of sterically strained conformers 1-s-*cis* and 1s-*trans* **6aa** may also be induced by crystal packing. In order to verify this assumption, the geometry of both isomers was optimized by the MP2/aug-cc-pvdz method. These calculations demonstrate that both isolated conformers are planar and very strained (see Supplementary Information). This supports the conclusion that the conformation of these isomers is determined mainly by conjugation. Bond lengths in both conformers are very close except for the N(1)-C(1) bond. The N(1)-C(1) bond is slightly shorter in conformer 1s-*trans* **6aa**, and the amino group has a planar configuration (the sum of the bond angles around the nitrogen atom is 360.0°). In the contrary, the N(1)-C(1) bond in conformer 1s-*cis* **6aa** is longer and the amino group has a more pyramidal configuration (the sum of the bond angles is 343.7°). This indicates that the amino group in 1s-*cis* **6aa** is participating in a lesser degree in conjugation. This also leads to the lower stability of 1s-*cis* **6aa** as compared to 1s-*trans* **6aa** by 4.86 kcal/mol.

Notably, there are considerable differences between experimental and calculated values for bond lengths of both conformers. This indicates that intermolecular interactions in the crystal phase provide a significant contribution to polarization of the molecules under consideration.

Conclusions

Contrary to previous reports,[16,17] the reaction of 4-(dimethylamino)but-3-en-2-one **1a** with malonodinitrile **2a** proceeded as shown in Schemes 1 and 3. As a first reaction product, 1-s-*cis*-(2*E*,4*E*)-2-cyano-5-(dimethylamino)hexa-2,4-dienamide (1-s-*cis* **6aa**) was isolated, which can be

converted into conformer 1-s-*trans* **6aa**. The structures of amides 1-s-*cis* **6aa** and 1s-*trans* **6aa** have been unambiguously proven by single crystal X-ray diffraction analyses. Treatment of amide 1-s-*cis* **6aa** with hydrochloric acid afforded 6-amino-2-oxo-1,2-dihydropyridine-3-carbonitrile **3aa**.

Experimental Section

General. Starting materials were used as obtained from commercial suppliers. Melting points were determined with a Kofler apparatus. ^{1}H and ^{13}C NMR spectra (DMSO-d_6 solutions) were recorded on a Varian Mercury VX-200 spectrometer. GC-MS was performed on a Varian 1200 L GC-MS instrument (EI, 70 eV). IR Spectra (KBr pellets) were taken with a Spectrum ONE Spectrophotometer. Elemental analysis was carried out on an EuroVector EA-3000 instrument. UV/Vis absorption spectra were recorded on Perkin Elmer Lambda 35 spectrometer. Microwave irradiation in sealed vials was carried out using Emrys^{TM} Creator EXP from Biotage (Uppsala). CCDC 743445 and CCDC 743446 contain the supplementary crystallographic data for 1-s-*cis* **6aa** and 1-s-*trans* **6aa**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

4-(Dimethylamino)but-3-en-2-one 1a.[16] A mixture of *N*,*N*-dimethylformamide dimethylacetal (DMFDMA, 7.15 g, 60.0 mmol) and acetone (8 mL) in a 20 mL microwave process vial was irradiated (absorbance level "Normal", 300 W initial power) at 150 °C (9 bar maximal pressure during the irradiation) for 15 min; the reaction was monitored by GC/MS. After irradiation was finished, the volatile components were removed under reduced pressure and the remaining oil (4.32 g, 64%) was used without purification for further reaction. MS: *m/z* (%) 113 (100, M^+), 98 (59.3), 82 (13.6), 70 (65.9), 55 (65.8).

1-s-*cis*-(2*E*,4*E*)-2-Cyano-5-(dimethylamino)hexa-2,4-dienamide (1-s-*cis* 6aa). To a mixture of 4-(dimethylamino)but-3-en-2-one (**1a**, 1.9 g, 16.8 mmol) and malonodinitrile (**2**, 1.12g, 17.0 mmol) in absol. EtOH (3 mL) was added piperidine (0.1 mL). The reaction mixture was stirred at room temperature for 4 h and left without stirring at room temperature for 24 h. The red crystalline precipitate was filtered off; a crystal was immediately subjected to X-ray analysis. The product was washed with EtOH (1.0 mL) and dried on air yielding crude 1-s-*cis* **6aa** (2.22 g, 74%); mp 217–218 °C. IR (KBr): $\tilde{\nu}$ 3412, 3152, 2188, 1657, 1575, 1344, 1276 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.92 (1H, d, J = 13.0 Hz, CH), 6.88 (2H, br s, NH_2), 5.34 (1H, d, J = 13.0 Hz, CH), 3.07 (6H, s, NMe_2), 2.18 (s, 3H, CH_3).

1-s-*trans*-(2*E*,4*E*)-2-Cyano-5-(dimethylamino)hexa-2,4-dienamide (1-s-*trans* 6aa). The red crystals 1-s-*cis* **6aa** were recrystallized from acetic acid affording a yellow crystalline precipitate 1-s-*trans* **6aa** that was used as such for X-ray analysis. The product was then washed with water

(1.0 mL) and dried at 100 °C affording a yellow solid **6aa** (after this treatment, the conformation of the product has not been checked again); mp 230–233 °C. IR (KBr): $\tilde{\nu}$ 3412, 3149, 2188, 1657, 1578, 1344, 1276, 1033 cm^{-1}. UV (MeOH): λ_{max} 394 nm (log ε = 4.57). The ^{1}H NMR spectrum is identical to that of crude 1-s-*cis* **6aa**. ^{13}C NMR (50 MHz, DMSO-d_6): δ 166.4, 163.1, 150.8, 119.9, 95.9, 87.8, 41.1, 16.2. Anal. calcd. for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.45; H, 7.03; N, 23.33. These data correspond to those reported in the literature for the alleged products **4aa**[17] (mp 228 °C, ^{1}H NMR) and **8aa**[16] (IR, ^{1}H and ^{13}C NMR).

6-Methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3aa)

Procedure A. A solution of 1-s-*cis* **6aa** (0.62 g, 3.5 mmol) in acetic acid and hydrochloric acid (37%) (2:1 v/v, 6 mL) was refluxed for 1h. After cooling, the crystalline precipitate formed was filtered off, washed with ethanol, and dried to give a colorless crystalline powder **3aa** (0.30 g, 65%). An analytical sample was recrystallized from water/acetone (1:1); mp 288–291 °C (decomp.) (lit.[19] mp 294–296 °C, decomp.; lit.[20] mp 285 °C, decomp.; lit.[22] mp 286 °C, decomp.). IR (KBr): $\tilde{\nu}$ 3460, 2851, 2223, 1661, 1583, 1439, 1326, 629. cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.55 (1H, br s, NH), 7.99 (1H, d, J = 7.3 Hz, CH), 6.18 (1H, d, J = 7.3 Hz, CH), 2.24 (3H, s, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 161.3, 154.4, 149.3, 117.3, 105.6, 100.3, 19.8. The spectral data match those reported.[22] The ^{1}H NMR spectral data closely match those reported in the literature for the alleged products **9aa**[16] and **10aa**.[17]

Procedure B. In a 20 mL microwave vial, a solution of 2-cyanoacetamide (**2c**, 2.52 g, 30.0 mmol) in water (10 mL) of was added to 4-(dimethylamino)but-3-en-2-one (**1a**, 3.39 g, 30.0 mmol**)**. The mixture was subjected to microwave irradiation at 175 °C for 5 min (absorbance level "Normal", 300 W initial power, 20 bar maximal internal pressure). The crystalline precipitate formed was filtered off, washed with water and acetone to give a colorless crystalline powder **3aa** (1.19 g, 33%). The spectral data match those of **3aa** obtained by procedure A.

Supplementary Information

Copies of spectra, X-ray diffraction experimental part and results of quantum-chemical calculations (MP2/aug-cc-pvdz method) for 1-s-*cis* **6aa** and 1-s-*trans* **6aa** are available as Supporting Information.

Acknowledgements

We kindly thank Dr. Valeriy V. Vashenko (SSI "ISC") for his help with GC/MS analyses.

References

1. Torres, M; Gil, S; Parra, M. *Curr. Org. Chem*. **2005**, *9*, 1757.
2. Pemberton, N.; Chorell, E.; Almqvist, F. *Top. Heterocycl. Chem.* **2006**, *1*, 1.
3. Robert, N.; Verrier, C.; Hoarau, C.; Celanire, S.; Marsais, F. *Arkivoc* **2008**, (*vii)*, 92.
4. Dawood, K. M.; Farag, A. M.; Khedr, N. A. *Arkivoc* **2008**, (*xv)*, 166.
5. Gorobets, N. Y.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. *Tetrahedron* **2004**, *60*, 8633.
6. Dzhavakhishvili, S. G.; Gorobets, N. Yu.; Chernenko, V. N.; Musatov, V. I; Desenko, S. M. *Izv. Akad. Nauk (Ser. Khim.)* **2008**, 412.
7. Yermolayev, S. A.; Gorobets, N. Yu.; Lukinova, E. V.; Shishkin, O. V.; Shishkina, S. V.; Desenko, S. M. *Tetrahedron* **2008**, *64*, 4649.
8. Mosti, L.; Schenone, P.; Menozzi, G. *J. Heterocycl. Chem.* **1985**, *22*, 1503.
9. Ziegler, E.; Wolfbeis, O. *Z. Naturforsch*. **1976**, *31B*, 1519.
10. Bondavalli, F.; Bruno, O.; Presti, E. L.; Menozzi, G.; Mosti, L. *Synthesis* **1999**, 1169.
11. Bellassoued-Fargeau, M.-C.; Grafte, B.; Sacquet, M.-C.; Maitte, P. *J. Heterocycl. Chem.* **1985**, *22,* 713.
12. Trummer, I.; Ziegler, E.; Wolfbeis, O. S. *Synthesis* **1981**, *3,* 225.
13. Ryabova, S. Y.; Alekseeva, L. M.; Granik, V. G. *Khim. Geterotsikl. Soedin.* **1991**, 1199. *Chem. Heterocycl. Comp.* **1991**, *27,* 960.
14. Ryabova, S. Yu.; Trofimkin, Yu. I.; Alekseeva, L. M.; Khabarova, L. S.; Granik, V. G. *Khim. Geterotsikl. Soedin.* **1991**, 343. *Chem. Heterocycl. Comp.* **1991**, *27*, 278.
15. Otto, H. H.; Schmelz, H. *Arch. Pharm.* **1982**, *315*, 526.
16. Al-Mousawi, S. M.; George, K. S.; Elnagdi, N. H. *Pharmazie* **1999**, *54*, 571.
17. Eiden F., Herdeis C. *Arch. Pharm*. (Weinheim) **1978**, *311,* 287.
18. Preliminary reports on some results: Sedash, Yu. V.; Gorobets N. Yu.; Shishkina S. V.; Desenko S. M. "*Chemistry of Nitrogen Containing Heterocycles*", Kharkiv, Ukraine, 2006: Abstracts, p. 210 (on-line: http://cnh2006.iflab.kiev.ua/ukr/reports/show/?id=279).
19. Perez-Medina, L. A.; Mariella, R. P.; McElvain, S. M. *J. Am. Chem. Soc.* **1947**, *69*, 2574.
20. Binovi, L. J.; Arlt, H. G. *J. Org. Chem.* **1961,** *26,* 1656.
21. Azuma, Y.; Morone, M.; Nagayama, K., Kawamata, Y.; Sato, A. *Heterocycles* **2003**, *60*, 1461.
22. Fischer, C. B.; Polborn, K.; Steininger, H.; Zipse H. *Z. Naturforsch.* **2004**, *59B*, 1121.