

One-pot three-component synthesis of 3-cyano-4-methyl-2,6-dioxopyridine amino enones

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DOI: 10.1016/j.mencom.2015.03.019

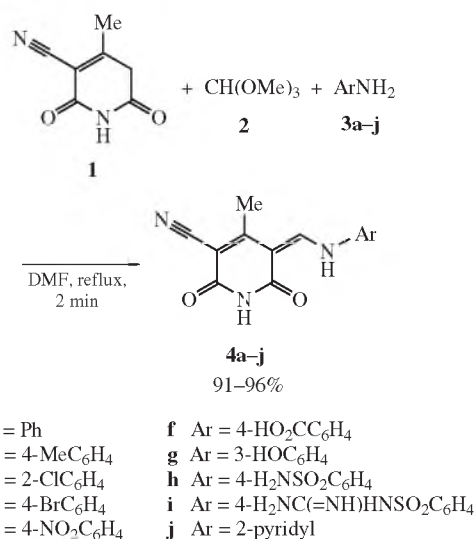
(*Z*)-5-(Arylaminoethylidene)-4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitriles were obtained by three-component condensation of 4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile with aromatic amines and trimethyl orthoformate in DMF. According to X-ray data, in the solid phase they exist as amino enone tautomers.

Interest in the three-component condensation of orthoformates, amines and active methylene compounds has been caused by a large diversity of the thus obtained amino enones.^{1,2} Bioactive amino enones were synthesized from derivatives of barbituric and thiobarbituric acids,³ oxindoles,⁴ pyrazolones^{4,5} and a number of other heterocycles.

However, pyridine-2,6-diones have not been explored in this reaction. These compounds are very promising due to their spectral and fluorescent properties⁶ and biological activity.⁷ Here we studied the reaction of 4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile with trimethyl orthoformate **2** and a number of aromatic amines **3a–j**.

Generally the condensation of ortho esters with a methylene and amine components is carried out by heating in acetic acid or another high boiling solvent in the presence of acid catalyst. We have shown that the use of DMF as a solvent without any catalyst simplifies this process to the level of click-procedure (Scheme 1).[†] In fact, the two-minute heating of the reactants in DMF is sufficient to complete the reaction with excellent yields. The precipitated crude product does not require further purification. Moreover, the reaction readily proceeds with both electron-donor and electron-acceptor substituted amines **3**, and stoichiometric ratio of the reactants is enough to achieve good yields of pure products.

Synthesized compounds **4a–j** may in principle exist as two tautomeric forms, amino enones **A** or hydroxy enimes **B** (Figure 1). Both of them are equally stabilized by intramolecular hydrogen bonds. However, signals of only one tautomeric form are observed in their ¹H NMR spectra. Unfortunately, on the basis of ¹H NMR spectra it is not possible to make an adequate choice between the forms. It is known that the azo dyes con-



Scheme 1

taining the 4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile moiety exist as hydrazone tautomers in solid phase and a DMSO solution.⁹ Structural similarity for tautomeric forms **A** of compounds **4a–j** and these azo dyes allowed us to suppose that compounds **4a–j** exist as amino enones. X-ray diffraction study of compound **4d** confirmed our assumption.

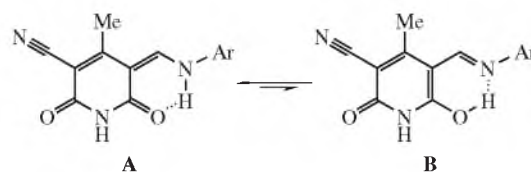


Figure 1 Potential tautomeric forms for compounds **4a–j**.

Two molecules of compound **4d** in the asymmetric part of the unit cell have the same tautomeric form (Figure 2).[‡] The C(1)–O(1) bond length corresponds to the double C=O bond with average value 1.231 Å¹⁰ and is rather far from single C–OH bond (av. 1.331 Å). The C(5)–C(8) bond length is much closer to that for double C=C bonds (1.376 Å) than for single C–C bonds in hydroxy enimes (1.434 Å).¹⁰ At the same time, lengths of the C(1)–C(5) and C(8)–N(1) bonds fully correspond to values

[†] General procedure. A mixture of 150 mg (1 mmol) of 4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile **1**, 0.09 ml (1 mmol) of aniline and 0.1 ml (1 mmol) of trimethyl orthoformate was heated in 0.3 ml DMF for 2 min. The yellow precipitate was filtered off and washed with DMF to give 0.24 g of (*Z*)-4-methyl-2,6-dioxo-5-(phenylaminoethylidene)-1,2,5,6-tetrahydropyridine-3-carbonitrile **4a**. Yield 94%. Yellow solid, mp 299–301 °C. ¹H NMR (200 MHz, DMSO-*d*₆) δ: 2.53 (s, 3H, Me), 7.29 (t, 1H, H_{Ar}, *J* 7.6 Hz), 7.46 (t, 2H, H_{Ar}, *J* 7.6 Hz), 7.62 (d, 2H, H_{Ar}, *J* 7.6 Hz), 8.58 (d, 1H, CH, *J* 12.8 Hz), 11.51 (s, 1H, NH), 12.97 (d, 1H, NH, *J* 12.8 Hz). MS (EI, 70 eV) *m/z*: 253 (M⁺). Found (%): C, 66.37; H, 4.39; N, 16.61. Calc. for C₁₄H₁₁N₃O₂ (%): C, 66.40; H, 4.38; N, 16.59.

Compounds **4b–j** were prepared similarly. For their characteristics, see Online Supplementary Materials.

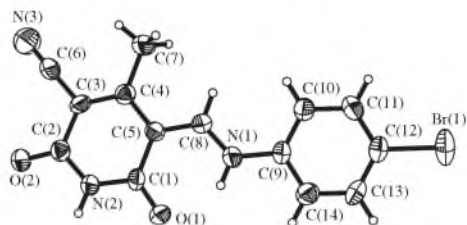


Figure 2 Structure of compound **4c** according to the X-ray diffraction data. Only one of two molecules in the asymmetric part of the unit cell is given. Selected bond lengths (Å): C(1)–O(1) 1.239(4), C(1)–C(5) 1.461(6), C(5)–C(8) 1.385(5), C(8)–N(1) 1.321(4) in the first molecule; and C(1A)–O(1A) 1.227(5), C(1A)–C(5A) 1.462(6), C(5A)–C(8A) 1.403(6), C(8A)–N(1A) 1.324(4) in the second one.

of the single bonds (1.446 Å for C–C and 1.332 Å for C–N, respectively¹⁰). These geometrical parameters unambiguously fit the amino enone tautomeric form (see Figure 1). The similarity of spectral and physico-chemical properties of compounds **4a–j** allows us to extend this assertion to all molecules in this series.

In summary, the one-pot three-component click-procedure for the synthesis of new 3-cyano-4-methyl-2,6-dioxypyridines

[‡] *Crystallographic data for 4d.* Crystals of C₁₇H₁₇BrN₄O₃ (*M* = 405.26) are monoclinic, *P*2₁/*n*, *a* = 13.7132(6), *b* = 13.2761(9) and *c* = 19.8463(13) Å, β = 95.129(5)°, *V* = 3598.7(4) Å³, *Z* = 8, *d*_{calc} = 1.496 g cm⁻³, μ = 2.308 mm⁻¹, *F*(000) = 1648. 30 154 reflections (6397 independent, *R*_{int} = 0.130) were collected on an Xcalibur-3 diffractometer (MoK α radiation, CCD-detector, graphite monochromator, ω -scanning, $2\theta_{\max}$ = 50°). Structure was solved by direct methods and refined against *F*² within anisotropic approximation for all non-hydrogen atoms by full-matrix least squares procedure using OLEX2 program package¹¹ with SHELXS and SHELXL modules.¹² All H atoms were placed in idealized positions [*d*(C–H) = 0.93–0.96 Å, *d*(N–H) = 0.86 Å] and constrained to ride on their parent atoms, with *U*_{iso} = 1.2*U*_{eq} (except *U*_{iso} = 1.5*U*_{eq} for methyl groups). Final refinement was converged at *wR*₂ = 0.0889 for all reflections [*R*₁ = 0.0602 for 2736 reflections with *F* > 4 σ (*F*), *S* = 0.96].

CCDC 1004677 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.

of amino enone type was accomplished with excellent yields in DMF without any catalysis. Further study of this procedure for the three-component condensation of other ortho esters, methylene active compounds and amines is underway.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.03.019.

References

- 1 L. A. Pavlova, Yu. A. Davidovich and S. V. Rogozhin, *Russ. Chem. Rev.*, 1986, **55**, 1026 (*Usp. Khim.*, 1986, **55**, 1803).
- 2 A.-Z. A. Elassar and A. A. El-Khair, *Tetrahedron*, 2003, **59**, 8463.
- 3 (a) A. Rauf, F. Ahmed, A. M. Qureshi, Aziz-ur-Rehman, A. Khan, M. I. Qadir, M. I. Choudhary, Z. H. Chohan, M. H. Youssoufi and T. Ben Hadda, *J. Chin. Chem. Soc.*, 2011, **58**, 528; (b) D. V. Pestov, V. I. Slesarev, A. I. Ginak and V. I. Slesareva, *Chem. Heterocycl. Compd.*, 1988, **24**, 782 (*Khim. Geterotsykl. Soedin.*, 1988, 952); (c) U. Huber, *US Patent US6573269 B1*, 2003.
- 4 O. S. Wolfbeis, *Monatsh. Chem.*, 1981, **112**, 369.
- 5 V. Colotta, L. Cecchi, F. Melani, G. Palazzino, G. Filacchioni, C. Martini, G. Giannaccini and A. Lucacchini, *J. Pharm. Sci.*, 1989, **78**, 239.
- 6 (a) J. Mirkovic, J. Rogan, D. Poleti, V. Vitnik, Z. Vitnik, G. Uscumlic and D. Mijin, *Dyes Pigments*, 2014, **104**, 160; (b) D. Mijin, G. Uscumlic, N. Valentic and A. Marinkovic, *Hem. Ind.*, 2011, **65**, 517.
- 7 L. A. Smyth, T. P. Matthews, P. N. Horton, M. B. Hursthouse and I. Collins, *Tetrahedron*, 2010, **66**, 2843.
- 8 L. Tietze und Th. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, Georg Thieme Verlag, Stuttgart, 1991 (in German).
- 9 (a) I. Ajaj, D. Mijin, V. Maslak, D. Brkovic, M. Milcic, N. Todorovic and A. Marinkovic, *Monatsh. Chem.*, 2013, **144**, 665; (b) K. M. Al-Zaydi, R. M. Borik and M. H. Elnagdi, *Ultrason. Sonochem.*, 2009, **16**, 660.
- 10 F. H. Allen, *Acta Crystallogr., Sect. B*, 2002, **58**, 380.
- 11 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.
- 12 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.