Mendeleev Communications

Mendeleev Commun., 2027, **37**, in press

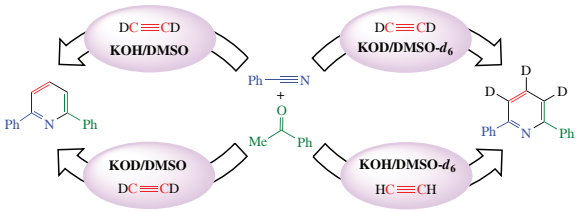
Deuterioacetylene as the mechanism tracer of self-organization of 2,6-diphenylpyridine-3,4,5-d_3 from benzonitrile and acetophenone

Elena Yu. Schmidt, Nadezhda V. Semenova, Igor A. Ushakov and Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: boris_trofimov@irioch.irk.ru

DOI: 10.71267/mencom.8121

The distribution of deuterium during the self-organization of 2,6-diphenylpyridine from benzonitrile and acetophenone in the C_2D_2/KOD/DOBu^t/DMSO-d_6 system evidences that the process is governed by dimsyl anions as actual superbases, representing the electron pair transfer between acetylenic carbanion, benzonitrile and acetophenone.



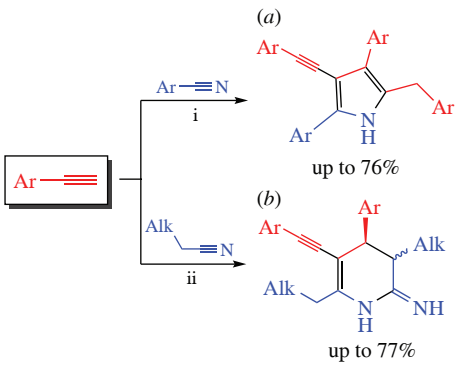
Keywords: acetylene, nitriles, ketones, pyridines, superbases.

Over the last two decades, the self-organization of complex molecules triggered by acetylene in the superbasic media gained considerable attention.[1,2] Acetylenes were found to unpredictably participate in multicomponent reactions involving simple and available starting compounds (ketones,[1] amines,[3] nitriles[4]) thereby affording the structures of higher complexity and diversity. Recent advances in this field include self-organization of tetrasubstituted pyrroles[5] and tetrasubstituted dihydropyridinimines[6] from nitriles and acetylenes in the KOBu^t/DMSO system, which demonstrated a strong response of the reaction to changes in the structure of a nitrile (Scheme 1). In the former case, an aromatic nitrile reacts with three molecules of arylacetylene to build up a substituted pyrrole ring [Scheme 1(*a*)].[5] In the latter case, two molecules of an aliphatic nitrile react with two molecules of arylacetylene to produce substituted dihydropyridinimines [Scheme 1(*b*)].[6]

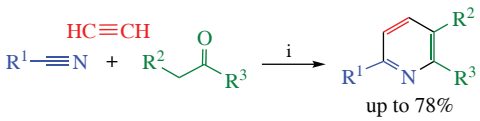
Recently we found that acetylene gas, various organic nitriles, and ketones produced a wide scope of di- and trisubstituted pyridines in good yields in the KOH/DMSO system (Scheme 2).[7]

In this work, to gain a deeper insight into the mechanism of this condensation, we have studied the reaction of deuterioacetylene gas (C_2D_2) with benzonitrile **1** and acetophenone **2** in the KOD/DOBu^t/DMSO and KOD/DOBu^t/DMSO-d_6 systems, giving 2,6-diphenylpyridine **3** and/or its deuterated analog, in order to track the deuterium distribution in the reaction components and thereby to retrieve additional information on their interactions during this process (Scheme 3).

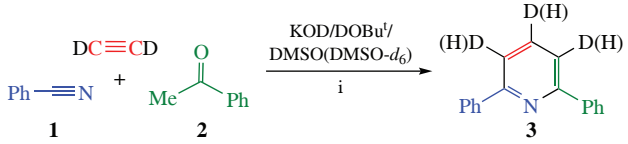
These experiments aimed to shed light not only on the mechanistic details of the process but also on the specific role of DMSO as an indispensable component of the superbasic composition, in which the self-organization phenomenon is the most pronounced. *A priori*, a number of different reactions should occur in the multicomponent system acetylene/benzonitrile/acetophenone/KOH/DMSO. These include the addition of acetylenic carbanions to the carbonyl group (synthesis of propargyl alcohols and diols),[8] the addition of acetophenone as CH-acid to acetylene (synthesis of bicyclooctanes),[1] the addition of acetylenic anions to the nitrile function (synthesis of acetylenic imines),[9] the self-condensation of acetophenone, alkaline hydrolysis of benzonitrile to benzamide and benzoic acid, *etc.*, as well as follow-up reactions of primary products. Surprisingly, among these expected parallel and crossover transformations, there is a dominant one, namely, the self-organization of 2,6-diphenylpyridine **3**. Generally, this is typical for all other known cases of acetylene-induced condensations. Therefore, it was reasonable to use labeled acetylene (C_2D_2) to better



Scheme 1 *Reagents and conditions*: i, KOBu^t, DMSO, room temperature, 15 min; ii, KOBu^t, DMSO, 40 °C, 5 h.



Scheme 2 *Reagents and conditions*: i, KOH, DMSO, 75 °C, 15 min, acetylene pressure ~3 atm.



Scheme 3 *Reagents and conditions*: i, KOBu^t, D_2O, DMSO (or DMSO-d_6), 75 °C, 2 h.

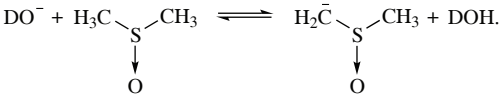
© 2027 Mendeleev Communications

understand its triggering and driving role in this and similar processes.

The first experiment was conducted with unlabeled reactants, except for the addition of D_2O (1 equiv. relative to benzonitrile **1**) to the reaction mixture under the previously established conditions (75 °C, 15 min, acetylene pressure ~3 atm).[7] Astonishingly, the isolated pyridine **3** (60% yield) contained no deuterium at all (^{1}H NMR, MS). This may be explained by a limited exchange of the reactant protons with the external medium during the concerted cyclization or by a larger amount of protons (compared to deuterons from D_2O) supplied by C_2H_2, CH_3 group of acetophenone **2** and CH_3 groups of DMSO. Another explanation of this fact is that D_2O is bound by solid KOH, which is poorly soluble in DMSO.

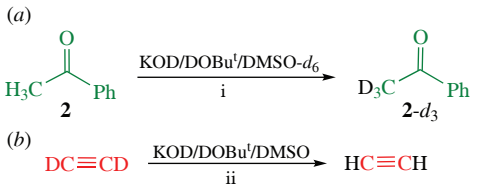
DMSO is known to generate dimsyl anions under treatment with strong bases (NaH, NaHMDS, KOBu^t, CsOH).[10–14] To our knowledge, this transformation was not commonly accepted for the KOH/DMSO system, although it was assumed by default. Dimsyl anions generated in the KOH/DMSO system were reported to react with ketones, affording allyl alcohols with an extra methylene group.[15]

Even more astonishing was the result of the experiment with C_2D_2 in the KOH/DMSO system, in which the isolated pyridine **3** (48% yield) turned out to be also free of deuterium. This can only occur if the H/D exchange rate is very high and the number of protons considerably exceeds that of deuterons, *i.e.* if the protons of DMSO are also involved in the process. Any remaining doubt about this conclusion was dispelled when the reaction was performed in the C_2D_2/KOD/DOBu^t/DMSO system, wherein DMSO was the only proton supplier, and the isolated pyridine **3** (40% yield) again contained no deuterium. Thus, the rapid formation of dimsyl anions in the composition studied should be considered experimentally proven, and, consequently, the following equilibrium should be quickly reached in the system:



Eventually, when the reaction with C_2D_2 was carried out in the fully deuterated composition KOD/DOBu^t/DMSO-d_6, the expected pyridine **3**-d_3 (3,4,5-d_3 isotopomer) was obtained in 44% yield with 100% selectivity (no protons were detected in product **3** by both NMR and MS spectra) (see Scheme 3). Thus, the self-organization of pyridine **3**-d_3 consumes the deuterium atoms delivered by DMSO-d_6 *via* the formation of dimsyl anions, which play a leading role in the whole process.

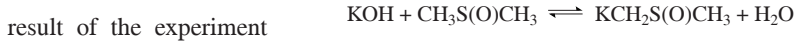
Next, it was necessary to check whether proton–deuterium exchange could occur in target product **3**. Non-deuterated pyridine **3** was treated with fully deuterated superbasic composition KOD/DOBu^t/DMSO-d_6 under the reaction conditions. As a result, no deuterium was detected (^{1}H NMR) in the pyridine ring. On the contrary, the starting acetophenone **2** in the same composition predictably exchanged its methyl protons for deuterium [Scheme 4(*a*)]. This confirms the facile formation of acetophenone carbanions and their active participation in the pyridine self-organization, *i.e.*, acetophenone reacted as CD_3 isotopomer. In the KOD/DOBu^t/DMSO composition, the rapid H/D exchange was experimentally observed for gaseous deuterioacetylene [Scheme 4(*b*)].



Scheme 4 *Reagents and conditions*: i, KOBu^t, D_2O, DMSO-d_6, 75 °C, 1 h; ii, KOBu^t, D_2O, DMSO, 25 → 75 °C, 30 min.

In line with the above observations was the selective formation of pyridine **3**-d_3 (45% yield) from C_2H_2, benzonitrile **1**, and acetophenone **2** in the composition KOH/HOBu^t/DMSO-d_6, wherein the only source of deuterium was deuterated DMSO. This result is consistent with the known application of the KOH(KOBu^t)/DMSO-d_6 system for deuteration of organic compounds.[16–19] Also, it is possible that observed deuterium incorporation could also occur from rapid equilibration among the anionic intermediates (*cf.* Scheme 5) generated in the reaction course.

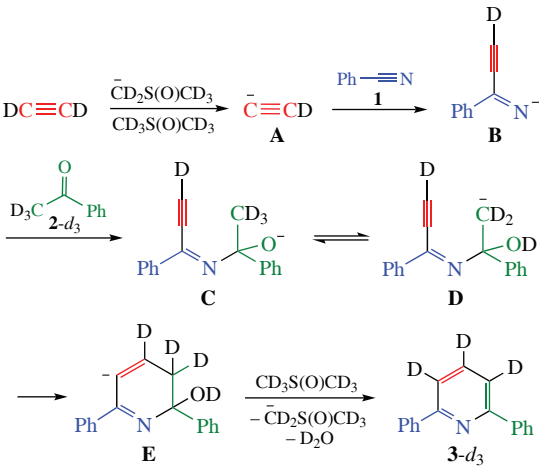
Evidently, the previous consideration of the KOH/DMSO system needs to be revised, as it has been proven here that DMSO is not just a solvent but also a reagent and a source of true superbase species (dimsyl anions). We assumed that despite the higher acidity of water compared to DMSO (pK_a 31.4[20] and 35.1,[21] respectively), the equilibrium



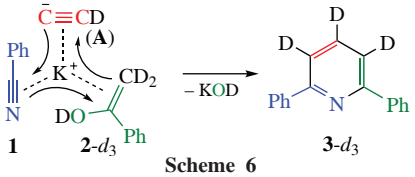
may be shifted to the right, likely due to the deactivation of water molecules by the complexation with an excess DMSO or due to the water uptake by the solid KOH, which is poorly soluble in DMSO.

All the above supports the previous assumption[7] that the self-organization of pyridine **3** is triggered by the acetylenic carbanion **A** (see Scheme 5), which attacks the C≡N bond of benzonitrile **1**. Formed acetylenic imine anion **B** further adds to the carbonyl group of acetophenone **2**. The anion **C** undergoes proton transfer (form **D**) and 6-*endo-dig* cyclization. Protonation (deuteration) and elimination of D_2O molecule of dihydropyridine anion **E** affords pyridine **3**-d_3. The absence of the 5-*exo-dig* product from cyclization of carbanion **D** is most likely a consequence of selective hyperconjugative stabilization of the 6-*endo-dig* pathway through donation from the carbanion into the σ*C–N orbital, similar to the previously documented regioselectivity.[22]

Since no intermediate was detected (^{1}H NMR) in the reaction mixture, an alternative hypothesis of the pyridine self-organization as a concerted process may be considered (Scheme 6).[7] This mechanism should involve transfer of the electron pair of the acetylenic carbanion **A** to the back of the same species **A** *via* electrophilic cyano and carbonyl groups (without formation of the kinetically independent intermediates) like a snake biting its tail. The acetylenic carbanion is necessarily escorted by potassium cation, which further accompanies the



Scheme 5



1 **2**-d_3 **3**-d_3

Scheme 6

anion transfer up to the carbonyl group. These three reacting molecules should be centripetal thereby facilitating the ring closure.

In summary, the character and dynamics of deuterium distribution during the self-organization of 2,6-diphenylpyridine-3,4,5-d_3 from deuterioacetylene, benzonitrile, and acetophenone in the KOH/DMSO system and its deuterated analogs evidence that the proton transfers and anion evolutions in this process are governed by dimsyl anions, which are generated *via* the deprotonation of DMSO. This conclusion is most likely extendable to other reactions that proceed in the KOH/DMSO systems.

This work was supported by the Russian Science Foundation (grant no. 24-13-00031). The spectral data were obtained with the equipment of the Baikal Analytical Center for collective use, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8121.

References

1 B. A. Trofimov and E. Yu. Schmidt, *Acc. Chem. Res*., 2018, **51**, 1117; https://doi.org/10.1021/acs.accounts.7b00618.
2 N. M. Vitkovskaya, V. B. Orel, V. B. Kobychev and A. S. Bobkov, *Russ. J. Org. Chem*., 2023, **59**, 1660; https://doi.org/10.1134/S1070428023100020.
3 E. Yu. Schmidt, N. V. Semenova, I. A. Ushakov, A. V. Vashchenko and B. A. Trofimov, *Org. Lett*., 2021, **23**, 4743; https://doi.org/10.1021/acs.orglett.1c01460.
4 E. Yu. Schmidt, N. V. Semenova, E. A. Golub', I. A. Ushakov and B. A. Trofimov, *Mendeleev Commun*., 2025, **35**, 636; https://doi.org/10.71267/mencom.7801.
5 E. Yu. Schmidt, I. V. Tatarinova, N. A. Lobanova, I. A. Ushakov, I. Yu. Bagryanskaya and B. A. Trofimov, *Org. Biomol. Chem*., 2023, **21**, 7209; https://doi.org/10.1039/d3ob01311a.
6 I. V. Tatarinova, N. A. Lobanova, I. A. Ushakov, E. Yu. Schmidt, and B. A. Trofimov, *Org. Biomol. Chem*., 2025, **23**, 4537; https://doi.org/10.1039/D5OB00266D.
7 E. Yu. Schmidt, N. V. Semenova, E. A. Golub', I. A. Ushakov, A. S. Bobkov, Yu. A. Orlyuk and B. A. Trofimov, *Org. Lett*., 2026, **28**, 8060; https://doi.org/10.1021/acs.orglett.6c01962.
8 N. A. Danilkina, A. A. Vasileva and I. A. Balova, *Russ. Chem. Rev*., 2020, **89**, 125; https://doi.org/10.1070/RCR4902.
9 J. Ahmed, A. K. Swain, A. Das, R. Govindarajan, M. Bhunia and S. K. Mandal, *Chem. Commun*., 2019, **55**, 13860; https://doi.org/10.1039/C9CC07833A.
10 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc*., 1965, **87**, 1345; https://doi.org/10.1021/ja01084a033.
11 P. Haiss and K.-P. Zeller, *Org. Biomol. Chem*., 2011, **9**, 7748; https://doi.org/10.1039/C1OB05889D.
12 H. Chen, W. Dai, Y. Chen, Q. Xu, J. Chen, L. Yu, Y. Zhao, M. Ye and Y. Pan, *Green Chem*., 2014, **16**, 2136; https://doi.org/10.1039/C3GC42310G.
13 L. Pan, M. V. Cooke, A. Spencer and S. Laulhé, *Adv. Synth. Catal*., 2022, **364**, 420; https://doi.org/10.1002/adsc.202101052.
14 M. S. Tschopp, A. Tortajada and E. Hevia, *Angew. Chem., Int. Ed*., 2025, **64**, e202421736; https://doi.org/10.1002/anie.202421736.
15 B. A. Trofimov, L. N. Sobenina, A. I. Mikhaleva, A. M. Vasiltzov and O. V. Petrova, *Patent RU2078075C1*, 1995; https://patentimages.storage.googleapis.com/6b/ba/f0/7065dee757e238/RU2078075C1.pdf.
16 M. Patel, R. K. Saunthwal and A. K. Verma, *Acc. Chem. Res*., 2017, **50**, 240; https://doi.org/10.1021/acs.accounts.6b00449.
17 M. Patel, R. K. Saunthwal and A. K. Verma, *ACS Omega*, 2018, **3**, 10612; https://doi.org/10.1021/acsomega.8b01329.
18 S. Kumar, M. Patel and A. K. Verma, *Asian J. Org. Chem*., 2021, **10**, 2365; https://doi.org/10.1002/ajoc.202100405.
19 H. Xu, Z.-J. Jiang, Y. Jia, Y. Su, J.-F. Bai, Z. Gao, J. Chen and K. Gao, *J. Org. Chem*., 2024, **89**, 8468; https://doi.org/10.1021/acs.joc.4c00352.
20 W. N. Olmstead, Z. Margolin and F. G. Bordwell, *J. Org. Chem*., 1980, **45**, 3295; https://doi.org/10.1021/jo01304a032.
21 F. G. Bordwell, J. C. Branca, C. R. Johnson and N. R. Vanier, *J. Org. Chem*., 1980, **45**, 3884; https://doi.org/10.1021/jo01307a030.
22 S. F. Vasilevsky, T. F. Mikhailovskaya, V. I. Mamatyuk, G. E. Salnikov, G. A. Bogdanchikov, M. Manoharan, I. V. Alabugin, *J. Org. Chem*., 2009, **74**, 8106; https://doi.org/10.1021/jo901551g.

Received: 18th June 2026; Com. 26/8121

Contents entry

Deuterioacetylene as the mechanism tracer of self-organization of 2,6-diphenylpyridine-3,4,5-d_3 from benzonitrile and acetophenone

Elena Yu. Schmidt, Nadezhda V. Semenova, Igor A. Ushakov, Boris A. Trofimov

