Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2019, **29**, 622–624

Mendeleev Communications

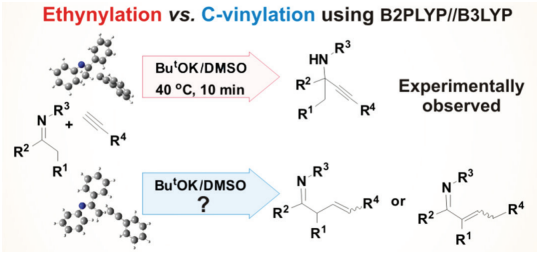
Quantum chemical comparison of ethynylation and C-vinylation routes in superbase catalyzed reaction of acetylenes with imines

Vladimir B. Orel,[a] Nadezhda M. Vitkovskaya,[a] Damir Z. Absalyamov,[a,b] Elena Yu. Schmidt[b] and Boris A. Trofimov*[b]

[a] *Laboratory of Quantum Chemistry, Irkutsk State University, 664003 Irkutsk, Russian Federation*
[b] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 395 241 9346; e-mail: boris_trofimov@irioch.irk.ru*

DOI: 10.1016/j.mencom.2019.11.005

The kinetic (free activation energies) and thermodynamic factors, which ensure mild conditions for the ethynylation of imines with acetylenes, have been established by quantum chemical calculations using B2PLYP/6-311+G//B3LYP/6-31+G*. According to the calculations, the alternative route of superbase catalyzed C-vinylation requires harsher reaction conditions as compared to the ethynylation one.**



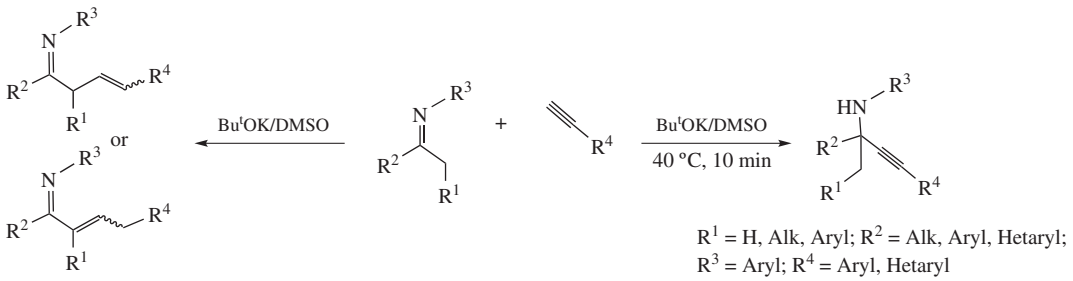
Propargylamines are flexible building blocks for organic synthesis and key structures of some natural products and drugs. Moreover, propargylamines are currently employed in the synthesis of numerous synthetically and pharmaceutically valuable heterocycles.[1]

Recently it has been found that arylacetylenes are capable of fast nucleophilic addition to imines in the Bu^{t}OK/DMSO superbase system under mild conditions (40 °C, 10 min) affording propargylamines in good to excellent yields (Scheme 1, right).[2]

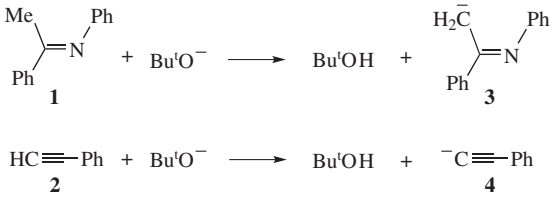
In this process, acetylenic carbanions add to the C=N bond, thereby formally featuring an aza type of the Favorsky reaction and opening new possibilities for organic synthesis. However, due to the dual electrophile–nucleophile reactivity of acetylenes, typically manifested in the superbase medium,[3] an alternative nucleophilic addition of imines as CH-acids to acetylenic C≡C bond, termed C-vinylation, is not excluded (Scheme 1, left), though the corresponding products have not been observed experimentally so far.

In this work, we used quantum chemical modeling of the two competing reactions of acetylenes with imines, namely the discovered ethynylation and possible C-vinylation, and evaluated computationally their kinetic and thermodynamic characteristics.

The quantum chemical calculations were carried out here in terms of the anionic model for the reaction of (*E*)-*N*,1-diphenylethanimine **1** with phenylacetylene **2**. The use of this model for another superbase catalyzed reaction allowed us earlier to estimate the competition between ethynide ion and ketone carbanion for the nucleophilic addition to the C=C bond of α,β-unsaturated ketones.[4] Here, the structural parameters as well as the vibrational corrections to enthalpies and Gibbs free energies of the investigated systems were calculated using B3LYP/6-31+G* approach.[5–7] Further, the energies at the stationary points were refined using the double hybrid functional B2PLYP/6-311+G**.[8] The above B2PLYP//B3LYP approach was also used for the calculation of the carbonyl group ethynylation and the ketone carbanion C-vinylation.[9] In this work, we checked as well the wave function stability for both ethynylation and C-vinylation transition states under the perturbations occurred. According to the calculations, the dispersion correction effect leads to the change in the relative thermodynamic stability for the starting compounds only by 0.4 kcal mol^{-1} and as well results in minor increase in the activation barriers with the difference up to 1.4 kcal mol^{-1} (Table S1, see Online Supplementary Materials). The solvation energy in DMSO medium was calculated additionally by the polarizable dielectric model using the integral equation formalism version of the Polarizable Continuum Method (IEFPCM).[10] To estimate activation free energy in solution, we used an approach based on the known results[11] and applied earlier to DMSO medium.[12] The calculations were carried out using the GAUSSIAN 09 program package[13] (for details, see Online Supplementary Materials).



Scheme 1

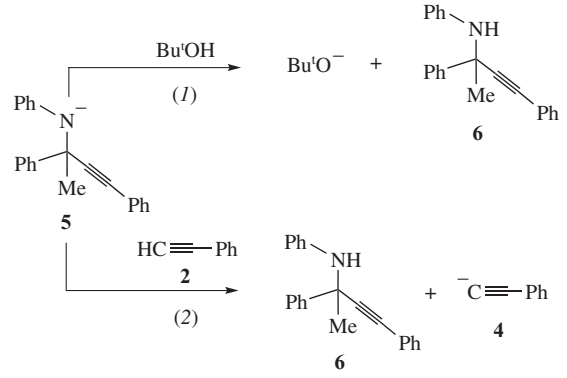


Scheme 2

At the first stage of the reaction investigated, the deprotonation of both imine **1** and phenylacetylene **2** can occur under the action of the superbase (Scheme 2).

According to our calculations, the proton transfer from the methyl group of imine **1** towards Bu^tO^- anion proceeds through the transition state $\mathbf{TS_{1\rightarrow3}}$ with an activation barrier $\Delta G^{\ddagger}$ = = 10.2 kcal mol^{-1}, generating imine carbanion **3** with the change in the system enthalpy ΔH = –0.4 kcal mol^{-1} (Figure 1). However, this deprotonation does not affect the free energy, ΔG = = 0.0 kcal mol^{-1}. Considering the deprotonation of acetylene **2** under the action of Bu^tO^- anion, it occurs without an activation barrier and leads to phenylethynide ion **4** with a decrease in enthalpy by 7.6 kcal mol^{-1} and in free energy by 2.1 kcal mol^{-1} (see Figure 1). Such an easy and thermodynamically favorable formation of anion **4** ensures its high concentration in the reaction medium, which further facilitates the ethynylation route.

Next, a nucleophilic addition of phenylethynide ion **4** to the imino carbon atom of compound **1** occurs through a transition state $\mathbf{TS_{4\rightarrow5}}$ (see Figure 1), affording nitrogen centered propargylamine anion **5**. The formation of intermediate **5** has the activation barrier $\Delta G^{\ddagger}$ = 20.9 kcal mol^{-1} and is accompanied by the change in enthalpy ΔH = –9.9 kcal mol^{-1} (ΔG = –1.2 kcal mol^{-1}) relative to the starting compounds.



Scheme 3

As follows further from the calculations, the protonation of anion **5** by Bu^tOH [Scheme 3, path (*1*)] gives propargylamine **6** and Bu^tO^- anion with an increase in enthalpy and Gibbs free energy (ΔH = 3.0 kcal mol^{-1}, ΔG = 2.9 kcal mol^{-1}). Indeed, the experimental acidity of aniline[14] in DMSO is by 1.5 pK_a units higher than the acidity of Bu^tOH.[15]

However, anion **5** can also be protonated by phenylacetylene **2** [Scheme 3 path (*2*)], whose acidity in DMSO is by 3.5 pK_a units higher than that of Bu^tOH.[14,16] In this instance, the formation of propargylamine **6** is accompanied by the decrease in energy (ΔH = –13.0 kcal mol^{-1}, ΔG = –7.5 kcal mol^{-1}) and the regeneration of phenylethynide ion **4**, which maintains its high concentration.

Thus, both the high concentration of the phenylethynide ion **4** and a relatively low barrier of the addition of phenylethynide ion **4** to the C=N bond of imine **1** (20.9 kcal mol^{-1}) explains the mild experimental conditions for the ethynylation route.[2] In addition, a high activation barrier for the decomposition of propargylamine

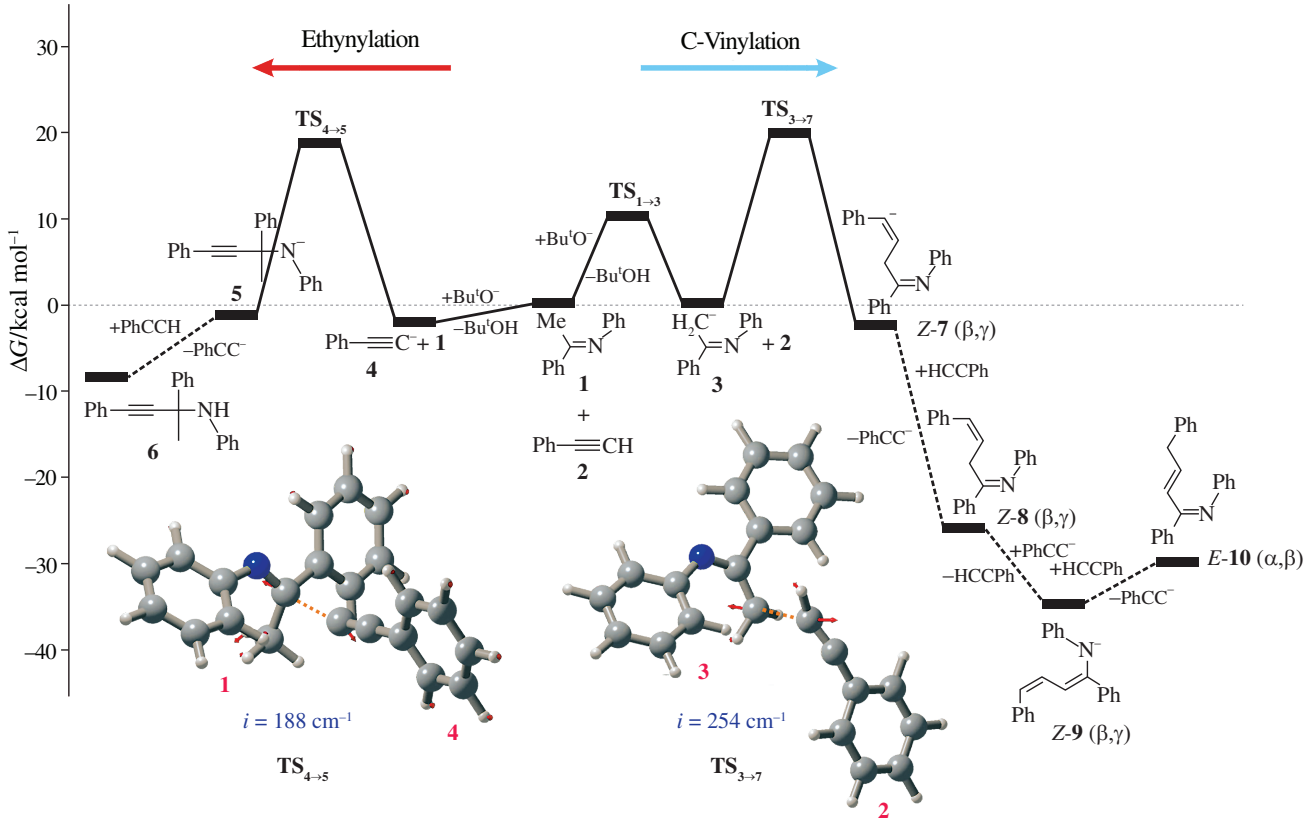


Figure 1 Profile of ethynylation and vinylation routes for the reaction of (*E*)-*N*,1-diphenylethanimine **1** with phenylacetylene **2**, indicating the corresponding transition states $\mathbf{TS_{4\rightarrow5}}$ and $\mathbf{TS_{3\rightarrow7}}$ with the formed bonds as dotted lines, displacement vectors as arrows and imaginary frequencies *i*.

6 ($\Delta G^{\ddagger}$ = 27.3 kcal mol^{-1}, see Figure 1) ensures its stability with elevation of the temperature.

The competing C-vinylation reaction can occur through the transition state $\mathbf{TS_{3\rightarrow7}}$ (see Figure 1), which corresponds to the nucleophilic addition of imine carbanion **3** to the triple bond of phenylacetylene **2**. Quantum chemical modeling demonstrates that the transformation of phenylethynide ion **4** and imine **1** into phenylacetylene **2** and imine carbanion **3** proceeds *via* an activation barrier $\Delta G^{\ddagger}$ = 12.3 kcal mol^{-1}, which is significantly lower than the activation barriers for both ethynylation and C-vinylation routes. Therefore, the contribution of a particular reaction pathway to the whole process is determined by the Curtin–Hammett principle,[17,18] *i.e.* exclusively by the relative energies of the corresponding transition states. As follows from the calculations, the free energy for the C-vinylation transition state $\mathbf{TS_{3\rightarrow7}}$ is higher than that for the ethynylation transition state $\mathbf{TS_{4\rightarrow5}}$ by 0.9 kcal mol^{-1} (see Figure 1). The dispersion correction leads to the additional increase in the difference of the activation barriers by 1.2 kcal mol^{-1}, making the ethynylation process kinetically preferable.

Note that the phenylacetylene molecule in the transition state $\mathbf{TS_{3\rightarrow7}}$ has *trans*-distorted configuration, which results in the formation of carbanion (*Z*)-**7**. Indeed, we demonstrated that vinylation by phenylacetylene occurs only through a transition state with a *trans*-distorted structure of the acetylene moiety.[19] According to our calculations, the formation of structure (*Z*)-**7** leads to the enthalpy lowering by 14.9 kcal mol^{-1} relative to isolated structures **1** and **2**. Protonation of carbanion (*Z*)-**7** by phenylacetylene **2** is accompanied by significant decrease in enthalpy relative to initial compounds **1** and **2** (ΔH = –32.7 kcal mol^{-1}), leading to the formation of β,γ-unsaturated imine (*Z*)-**8** and phenylethynide ion **4**. 1,3-Prototropic rearrangement of imine (*Z*)-**8** *via* the intermediate anion (*Z*)-**9** affords α,β-unsaturated imine (*E*)-**10** with decrease in enthalpy by 2.7 kcal mol^{-1}. The generation of the unsaturated imines (*Z*)-**8** and (*E*)-**10** is thermodynamically favorable compared with the formation of propargylamine **6** by 19.7 and 22.4 kcal mol^{-1}, respectively.

In summary, the quantum chemical modeling has revealed that the ethynylation of imine **1** with phenylacetylene **2** is associated with an activation barrier $\Delta G^{\ddagger}$ = 20.9 kcal mol^{-1} and can be accomplished by protonation of the nitrogen centered anion **5** by phenylacetylene **2**, resulting in the thermodynamically stable propargylamine **6** (ΔG = –7.5 kcal mol^{-1}) and phenylethynide ion **4**, which in turn continues the ethynylation of imine **1**. These factors ensure the discovered easy ethynylation of ketimines with acetylenes at 40 ºC for 10 min.[2] On the contrary, the preferable formation of phenylethynide ion **4** compared with imine carbanion **3** (ΔG = 2.1 kcal mol^{-1}) as well as a significant activation barrier ($\Delta G^{\ddagger}$ = 27.3 kcal mol^{-1}) for the decomposition of propargylamine **6** impede the thermodynamically favorable C-vinylation of imine **1** by phenylacetylene **2**. Thus, the quantum chemical calculations indicate that the base promoted C-vinylation of imines by arylacetylenes would become possible under harsher reaction conditions.

The support by the Russian Science Foundation (project no. 19-13-00052) is acknowledged by B.A.T. and E.Yu.Sch., and the support by the Ministry of Education and Science of the Russian Federation (grant no. 4.1671.2017/4.6) and the Russian Foundation for Basic Research (grant no. 18-03-00573a) is acknowledged by N.M.V., V.B.O. and D.Z.A.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.005.

References

1 K. Lauder, A. Toscani, N. Scalacci and D. Castagnolo, *Chem. Rev.*, 2017, **117**, 14091.
2 I. A. Bidusenko, E. Yu. Schmidt, I. A. Ushakov and B. A. Trofimov, *Eur. J. Org. Chem*., 2018, 4845.
3 B. A. Trofimov and E. Yu. Schmidt, *Acc. Chem. Res*., 2018, **51**, 1117.
4 V. B. Kobychev, V. B. Orel, D. V. Zankov, N. M. Vitkovskaya and B. A. Trofimov, *Russ. Chem. Bull., Int. Ed.*, 2017, **66**, 2227 (*Izv. Akad. Nauk, Ser. Khim.*, 2017, 2227).
5 A. D. Becke, *Phys. Rev. A: At., Mol., Opt. Phys.*, 1988, **38**, 3098.
6 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785.
7 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
8 S. Grimme, *J. Chem. Phys.*, 2006, **124**, 034108.
9 N. M. Vitkovskaya, V. B. Orel, V. B. Kobychev, E. Yu. Schmidt and B. A. Trofimov, *Int. J. Quantum Chem.*, 2018, **118**, e25689.
10 J. Tomasi, B. Mennucci and E. Cancès, *J. Mol. Struct.: THEOCHEM*, 1999, **464**, 211.
11 D. H. Wertz, *J. Am. Chem. Soc*., 1980, **102**, 5316.
12 N. M. Vitkovskaya, V. B. Kobychev, A. S. Bobkov, V. B. Orel, E. Yu. Schmidt and B. A. Trofimov, *J. Org. Chem*., 2017, **82**, 12467.
13 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision C.01*, Gaussian, Inc., Wallingford, CT, 2009.
14 F. G. Bordwell and D. J. Algrim, *J. Am. Chem. Soc*., 1988, **110**, 2964.
15 W. N. Olmstead, Z. Margolin and F. G. Bordwell, *J. Org. Chem*., 1980, **45**, 3295.
16 F. G. Bordwell, G. E. Drucker, N. H. Andersen and A. D. Denniston, *J. Am. Chem. Soc*., 1986, **108**, 7310.
17 J. I. Seeman, *Chem. Rev.*, 1983, **83**, 83.
18 J. I. Seeman, *J. Chem. Educ*., 1986, **63**, 42.
19 V. B. Kobychev, N. M Vitkovskaya, V. B. Orel, E. Yu. Schmidt and B. A. Trofimov, *Russ. Chem. Bull., Int. Ed.*, 2015, **64**, 518 (*Izv. Akad. Nauk, Ser. Khim.*, 2015, 518).

Received: 16th May 2019; Com. 19/5926