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Synthesis of pyridinium ylides and simulation of their 1,3-dipolar cycloaddition mechanism

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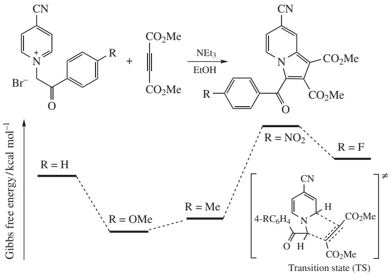
Synthesis of some pyridinium ylides with different 4-R-phenyl substituents (R = H, MeO, Me, NO$_2$, F) has been performed. Quantum-chemical calculations on the spatial and electronic structure, as well as the modeling of 1,3-dipolar cycloadddition reaction of these compounds have been carried out. The results of computer modeling are in good agreement with the results of the synthesis of these compounds.

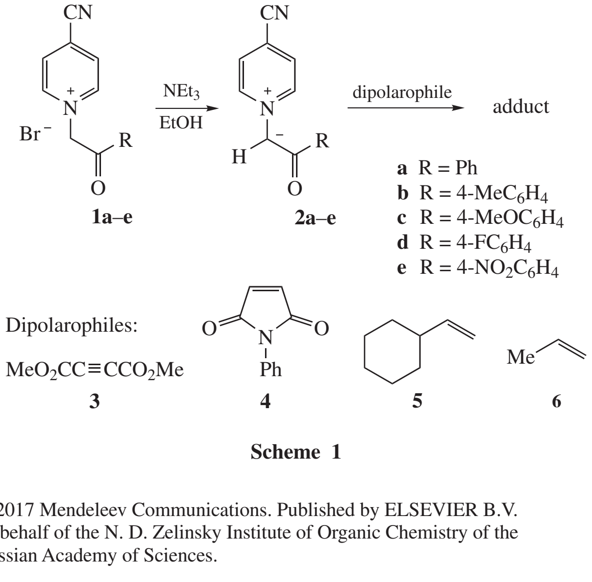


1,3-Dipolar cycloaddition is one of the most convenient methods for the synthesis of five-membered heterocycles.[1–10] Such an approach is also applied to the preparation of polymer systems.[11,12]

In this study, we focused on pyridinium ylides as 1,3-dipoles. Their precursors, quaternary pyridinium salts **1a–e**, were obtained by standard procedures[2,3] using α-bromoacetophenones bearing functional groups with different electronic influence (Scheme 1).

Ylides **2a–e** were generated *in situ* by the base (Et$_3$N) in ethanol solution (or suspension) in the presence of dipolarophile **3–6**. The opportunities of this reaction with participation of pyridinium ylide, however, were comparatively rarely used. This seems to be due to a poor knowledge of the mechanism for generation of such ylides. Therefore, evaluation of the influence of various electron-donating and electron-withdrawing substituents in phenylene fragments on the reactivity of pyridinium ylides **2a–e** in cycloaddition at various dipolarophiles both by means of preparative and quantum chemical methods looks topical.

First, 4-cyanopyridine derivatives were chosen as model compounds. In the preliminary experiments it was established that dimethyl acetylenedicarboxylate **3** was the most rational dipolarophile for studying the reactions of 1,3-dipolar cycloaddition. In the case of highly active *N*-phenylmaleimide **4** adduct yields for all **2a–e** exceed 90%, which would not allow us to evaluate the substituent effect. When vinylcyclohexane **5** was tested as a dipolarophile, cycloadducts were formed in trace amounts.



Scheme 1

To get more insight into the reaction nature, quantum chemical simulation of the transformations outlined in Scheme 1 was performed.

For this purpose, the DFT B3LYP method with the basis set 6-31+G(d) was used. The IEF-PCM method was applied to take solvent effect into account. The Hartree–Fock approximation with 6-311++G(2d,p) basis set was used to estimate the energies of the frontier molecular orbitals (FMOs).†

Figure 1 shows the calculated energy values of the frontier orbitals of pyridinium ylides – the lowest unoccupied (LUMO) and the highest occupied (HOMO). As follows, donor substituents in the aryl fragment increase the energy of the molecular orbitals (MO), whereas the acceptor ones decrease it. The solvent (ethanol), according to the calculations, increases the energy difference between HOMO and LUMO.

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† *Calculation Methods*. Optimization of the geometric structure was performed by the DFT method with the functional B3LYP[14] and basis 6-31+G(d) using the Gaussian 09[15] software package. To estimate the energies of the frontier molecular orbitals (FMOs), the Hartree–Fock approximation with 6-311++G (2d, p) basis set was used, since the calculation of the energies of occupied molecular orbitals (HOMO and LUMO), performed by the DFT method, as well as the use of minimal bases for estimating the energies of unoccupied MO, leads to inaccurate eigenvalues of orbitals.[16,17] The localization of the stable states of the molecules on the potential energy surface (PES) was estimated by the absence of negative vibrational frequencies of the corresponding minima of the PES. The presence of one of the negative values indicated the localization of the saddle points corresponding to the transition state (TS). The IEF-PCM[18] method was used to take the solvent (ethanol) into account.

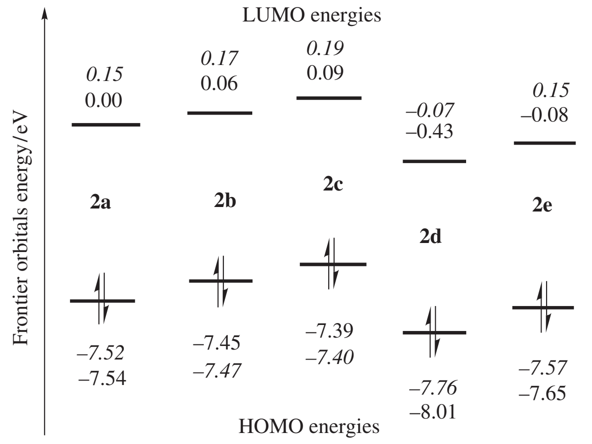


Figure 1 Energy of the frontier orbitals of pyridinium ylides. Hereinafter gas phase values are set in Roman and those for EtOH solution in italic type.

In addition, comparison of the energies of orbitals of substrate **2a** and dimethyl acetylenedicarboxylate **3** allows one to conclude that cycloaddition (Figure 2) leads to electron donation from the HOMO of the ylide to the LUMO of acetylenedicarboxylic acid dimethyl ester, and not *vice versa*. Hence, introduction of donor substituents into pyridinium ylides accelerates the reaction, while the introduction of acceptor ones slows it.

Based on the data obtained, one can assume that introduction of acceptor substituents into acetylene, on the contrary, should increase the product yield (and *vice versa*). The calculated data, on the whole, correlate well with the experimental results. Thus, when pyridinium salts **1a–e** react with dimethyl acetylenedicarboxylate **3**, the highest yields (58%) were achieved for methoxy compound **7c**, while the yield of nitro product **7e** was 34% (Scheme 2).[‡]

When comparing the values of the FMO energies of dipolarophiles (Figure 3), the closeness of the LUMO energies of these compounds is noticeable in contrast to the HOMO ones. However, as mentioned above, electron donation of the ylide HOMO to the dipolarophile LUMO occurs. One may conclude that electronic structure of these dipolarophiles is weakly related to their reactivity in the studied 1,3-dipolar cycloaddition reaction.

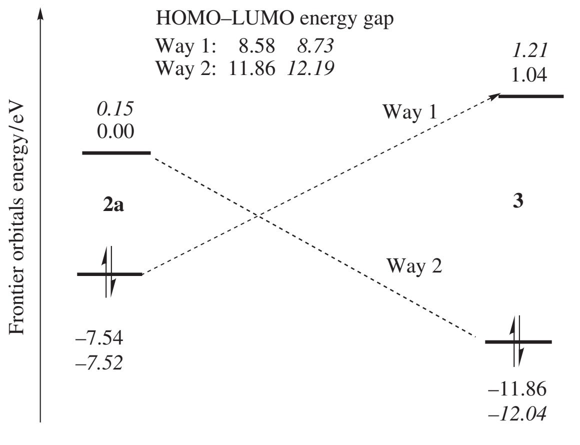
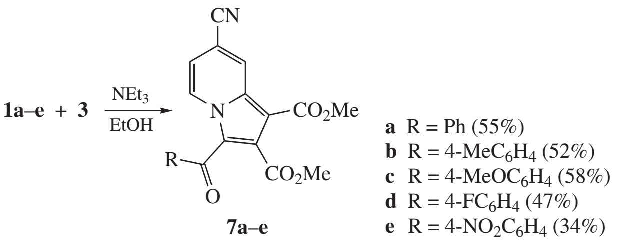


Figure 2 Energy of the frontier orbitals of reactants **2a** and **3**.



Scheme 2

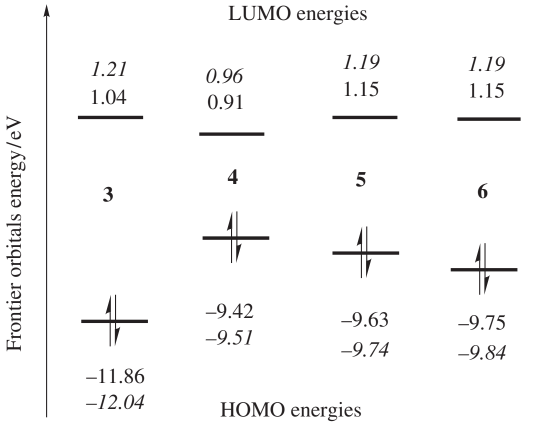
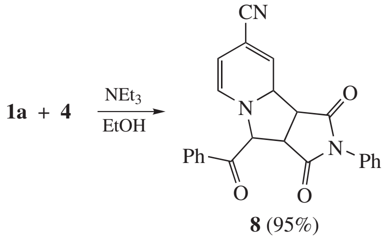


Figure 3 Energy of the frontier orbitals of dipolarophiles.

Analysis of the results presented in Figures 2 and 3 indicates that *N*-phenylmaleimide **4** should react more efficiently with pyridinium ylides than acetylenedicarboxylate **3** since the energy difference between HOMO of pyridinium and LUMO of **4** is much less than that for **3**. Experimental data show that product **8** is formed in the reaction between pyridinium salt **1a** and **4** in a yield of 95% (Scheme 3).



Scheme 3

Table 1 gives the calculated free Gibbs energies of the cycloaddition reaction to form an intermediate which is further decomposed to the final products according to Scheme 4. Note that the sum of the total Gibbs energies of the initial reagents (ylides and methyl acetylenedicarboxylate) is taken as zero.

From the results represented as diagrams of the dependence of Gibbs energies on substituents for the aryl group of pyridinium (Figure 4) it follows that the most energetically advantageous way of cycloaddition is the reaction of ylides containing electron-donor methoxy group, since the energy of the transition state (*i.e.*, the activation barrier) is the lowest in a series of compounds with the mentioned substituents, and the product formed is the most thermodynamically stable. An opposite result relates to electron-withdrawing nitro group. The rest of substituents locates between

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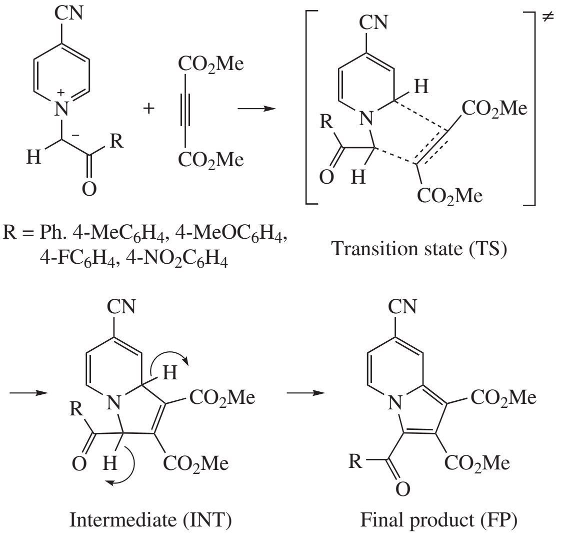
[‡] *1,3-Cycloaddition of pyridinium ylides to dimethyl acetylenedicarboxylate* **3** *(general procedure)*. Triethylamine (4.0 mmol) was added dropwise with stirring to the mixture of quaternary salt **1a–e** (3.3 mmol) and alkyne **3** (4 mmol) in ethanol (20 ml) at 20 °C. The mixture was left for 24 h, then precipitate of adduct **7a–e** was filtered, washed with EtOH and dried in air at room temperature.

Dimethyl 7-cyano-3-(4-methoxyphenyl)indolizine-1,2-dicarboxylate **7c**. Yield 58%, red solid, mp 152–153 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (s, 3H, CO_2Me), 3.86 (s, 3H, CO_2Me), 3.89 (s, 3H, MeO), 7.05 (d, 2H, H_{Ar}, *J* 7.6 Hz), 7.46 (d, 1H, H_{Ar}, *J* 4.6 Hz), 7.68 (d, 2H, H_{Ar}, *J* 7.6 Hz), 8.71 (s, 1H, H_{Ar}), 9.12 (d, 1H, H_{Ar}, *J* 4.6 Hz). MS (EI), *m/z*: 392 $[M]^+$.

For characteristics of compounds **7a**,**b**,**d**,**e** and **8**, see Online Supplementary Materials.

Table 1 Free Gibbs energies ($\Delta_r G$) of cycloaddition reaction and final products (see Scheme 4).

R	$\Delta_r G$/kcal mol^{-1}					
	Gas phase		Solution (EtOH)		ΔG^0 (FP)	$\Delta G^0_{\mathrm{INT}}$ (FP)
	TS	INT	TS	INT		
Ph	24.0	–17.1	24.7	–13.6	–51.4	–34.4
4-MeOC$_6$H$_4$	23.4	–17.9	24.3	–14.8	–51.9	–34.0
4-MeC$_6$H$_4$	23.5	–17.5	24.4	–14.3	–51.6	–34.1
4-NO$_2$C$_6$H$_4$	24.4	–14.6	25.8	–10.7	–50.1	–35.4
4-FC$_6$H$_4$	23.9	–16.7	24.9	–13.4	–51.3	–34.6



Scheme 4

methoxy and nitro groups by the impact exerted on the energy of transition states and products, which correlates well with the calculated energies of the frontier orbitals (see Figure 4) and is in agreement with the calculated FMO energies (see Figure 1).

In general, the reaction of 1,3-dipolar cycloaddition with the studied substrates can be represented as the final stage in Scheme 4. Comparison of the free Gibbs energies of the final products (FP) with respect to the sum of the energies of the initial reactants and the intermediate (INT) (see Table 1) indicates that the most stable product is the methoxy substituted one, which is in accordance with the results of calculations presented above (Figure 4). The sum of the total Gibbs energies for ylides, acetylenedicarboxylate and a hydrogen molecule was taken as zero.

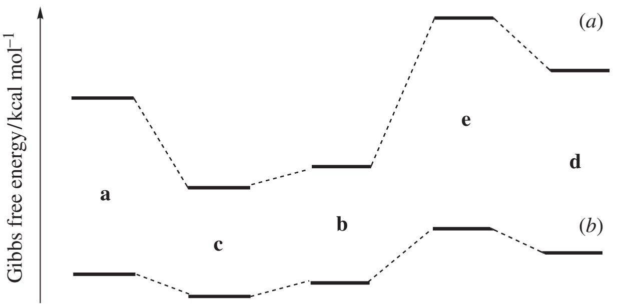


Figure 4 Influence of substituents on the Gibbs free energy of (*a*) TS and (*b*) INT.

Thus, experimental and quantum-chemical calculation data on the generation of a number of pyridinium ylides and their following 1,3-dipolar cycloaddition showed that the presence of electron-donating groups in pyridinium ylides provides the higher yields of products, whereas the introduction of electron-withdrawing groups slows down the reaction. The obtained data are somewhat different from those for close reactions of nitrile oxides and sulfides.[13]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.09.025.

References

1 A. Thakur and J. Louie, *Acc. Chem. Res.*, 2015, **48**, 2354.
2 F. Alonso, Y. Moglie and G. Radivoy, *Acc. Chem. Res.*, 2015, **48**, 2516.
3 V. P. Ananikov, E. A. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun.*, 2015, **25**, 75.
4 Z.-J. Zheng, D. Wang, Z. Xu and L.-W. Xu, *Beilstein J. Org. Chem.*, 2015, **11**, 2557.
5 W. Cieslik, M. Serda and R. Musiol, *Curr. Org. Chem.*, 2015, **19**, 1410.
6 Y. Ukaji and T. Soeta, *J. Synth. Org. Chem.*, 2015, **1**, 66.
7 P. N. Solyev, R. A. Novikov, M. K. Kukhanova and M. V. Jasko, *Mendeleev Commun.*, 2014, **24**, 206.
8 T. Gao, X. Chen, L. Jiang, M. Wu, H. Guo, J. Wang, S. Sun, J. Oiler and Y. Xing, *Eur. J. Org. Chem.*, 2016, 4957.
9 S. Bonte, I. O. Ghinea, R. Dinica, I. Baussanne and M. Demeunynck, *Molecules*, 2016, **21**, 332.
10 I. Yavari, J. Sheykhahmadi, M. Naeimabadi and M. R. Halvagar, *Mol. Divers.*, 2017, **21**, 1.
11 G. Delaittre, N. K. Guimard and C. Barner-Kowollik, *Acc. Chem. Res.*, 2015, **48**, 1296.
12 S. Hassan and T. J. J. Müller, *Adv. Synth. Catal.*, 2015, **357**, 617.
13 K. A. Chudov, N. D. Chuvylkin, D. V. Tsyganov, P. P. Purygin, N. Seeboth, A.-F. Salit, S. N. Ivanov and M. M. Krayushkin, *Russ. Chem. Bull., Int. Ed.*, 2016, **65**, 2978 (*Izv. Akad. Nauk, Ser. Khim.*, 2016, 2978).
14 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
15 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, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision A1*, Gaussian, Inc., Wallingford, CT, 2009.
16 D. H. Ess and K. N. Houk, *J. Am. Chem. Soc.*, 2008, **130**, 10187.
17 R. Stowasser and R. Hoffmann, *J. Am. Chem. Soc.*, 1999, **121**, 3414.
18 J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999.

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