Russian Journal of Organic Chemistry, Vol. 40, No. 6, 2004, pp. 775–789. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 6, 2004, pp. 816–829.

Reactions of Heterocumulenes with Organometallic Reagents: X.* Quantum-Chemical Study of the Reaction of Aliphatic Isothiocyanates with Lithiated Allenes. Intramolecular Rearrangements of 1,3,4-Azatrienes

V. A. Shagun[1], D-S. D. Toryashinova[1], N. A. Nedolya[1], O. A. Tarasova[1], and L. Brandsma[2]

[1] *Favorskii Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033, Russia*
e-mail: shagun@irioch.irk.ru

[2] *Utrecht University, Utrecht, the Netherlands*

Received October 29, 2003

Abstract—Study of the potential energy surface for the reaction of isothiocyanates with α-lithiated allenes showed that the formation of 1,3,4-azatriene occurs in one step through a four-center transition state. [1,5]-Sigmatropic rearrangements of 1,3,4-azatrienes and electrocyclizations of the resulting conjugated 1,3,5-azatriene systems lead to formation of dihydropyridine ring. Pyrrole structures are more likely to arise from protonation of 3-alkoxy-1,3,4-azatriene.

Until recently, reactions of organolithium compounds with isothiocyanates have been regarded mainly as a method for preparation of thioamides [2, 3], which has not received wide application for some reason [3]. As was shown for the first time in [4], analogous reactions of isothiocyanates with lithium derivatives of allenes and alkynes open almost unlimited prospects in the synthesis of previously unknown or difficultly accessible highly reactive conjugated heteropolyene systems like C=C=C–C=N (1,3,4-azatrienes) and C=C–C=C–N=C (1,3,5-azatrienes) and products of their intramolecular cyclization, e.g., pyrroles, dihydropyridines, quinolines, thiophenes, and other fundamental heterocyclic structures. Moreover, these reactions often provide the most efficient or the only method of synthesis of such compounds. It was found [4] that the results of experiments performed under similar conditions strongly depend on the structure of substituents in both isothiocyanate and lithiated allene or alkyne. Some illustrative examples are given below. The reaction of γ-lithiated 3-methyl-1,2-butadiene with methyl and ethyl isocyanates gives 6-alkylsulfanyl-3,3-dimethyl-2,3-dihydropyridines [4, 5]; from isopropyl, cyclopentyl, and cyclohexyl isothiocyanates, cyclobuta[1,2-*b*]pyrroles and pyridine-2(1*H*)-thione [4–6] are obtained; and the reaction with phenyl isothiocyanate yields 2-alkylsulfanyl-4-isopropylquinolines [4, 5, 7]. Analogous reactions of α-lithiated alkoxyallenes [e.g., methoxy-, *tert*-butoxy-, and 1-(1-ethoxyethoxy)allenes] with aliphatic isothiocyanates lead to formation of mixtures of the corresponding pyrroles and 2,3-dihydropyridines whose ratio is determined by the relative rates of two concurrent processes, intramolecular cyclization of intermediate 1,3,4-azatriene to pyrrole and [1,5]-sigmatropic rearrangement into 1,3,5-azatriene; electrocyclization of the latter gives rise to dihydropyridine; the rates of these processes depend in turn on the substituent at the nitrogen atom [4, 8–10]. Aromatic isothiocyanates react with α-lithiated alkoxyallenes to give mixtures of pyrroles and quinolines [4, 11]. The reactions of 1-lithio-1-alkoxyallenes with methoxymethyl isothiocyanate afford exclusively 2,3-dihydropyridines which are readily converted into the corresponding pyridines via elimination of methanol [12]; cyclopropyl isothiocyanate with 1-lithio-1-alkoxyallenes forms pyrrole derivatives [4]. In addition, numerous examples of further transformations of 1,3,4-azatrienes as primary reaction products have been reported; their direction depends on the nature of substituents both at the nitrogen atom and in the allene fragment [4].

* For communication IX, see [1].

1070-4280/04/4006-0775 © 2004 MAIK "Nauka/Interperiodica"

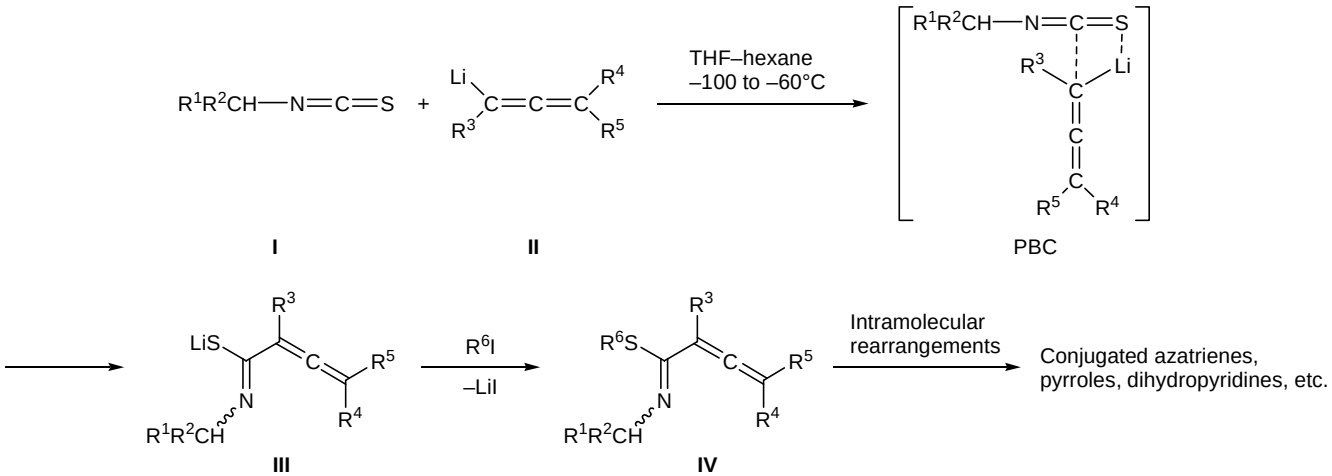
Naturally, the observed high sensitivity of this reaction to stereoelectronic effects of the initial reactants, intermediates, and final products needs to be explained not only on a qualitative level. It requires quantitative estimation of possible reasons and reaction mechanisms [4–12].

In the present work we made the first attempt to analyze by quantum-chemical methods some operational mechanisms (which were mainly hypothetical in the earliest studies [8–13]) of the reaction of isothiocyanates **I** with lithiated allenes **II**, both proved experimentally and still unconfirmed. In particular, we examined the potential energy surface for reactions of a series of isothiocyanates and lithiated allenes and determined kinetic and thermodynamic parameters of the addition. We also studied the conformational behavior and isomeric transformation of 1,3,4-azatriene as key intermediate and analyzed most probable ways of its intramolecular cyclization, both spontaneous and promoted by external factors.

Nonempirical calculations were performed at the HF and B3LYP levels with the 6-31G** basis set using GAUSSIAN-98 software [14]. Full geometry optimization of molecular systems corresponding to transition structures ($\lambda = 1$, where λ is the number of negative Hessian eigenvalues in a given stationary point [15]) and energy minima ($\lambda = 0$) on the potential energy surface (PES) was conducted up to a value of 10^{-5} a.u./bohr. While analyzing flat areas, the limiting gradient values were set at a level of 10^{-6} a.u./bohr with account taken of configurational mobility of the systems under study. The force constant matrix was calculated by a subprogram built in GAUSSIAN. Structures corresponding to energy minima on the PES were identified by the fastest descend technique while moving along the gradient line from a saddle point to the nearest critical point; a small initial shift along the transition vector was set, which allowed proper determination of the reaction path [15].

However, before proceeding to discussion of the results, brief information should be given on the reaction conditions (Scheme 1). Lithiation of allenes and alkynes, including those considered below, has been well documented [4, 16]. These reactions are usually carried out in a mixture of tetrahydrofuran (THF) with hexane using butyllithium as the most accessible deprotonating base. The reaction temperature and time are usually determined by the substrate structure. Deprotonation of unsubstituted allene is performed at –85 to –50°C; here, it should be kept in mind that at –10°C lithioallene **IIa** is converted into 1-lithio-1-propyne. Lithiation of alkoxyallenes [R^3 = OMe, OCH(Me)OEt, $R^4 = R^5$ = H] readily occurs at –100 to –60°C in 5–10 min, yielding α-lithiated intermediates **IIb** and **IIc** with high regioselectivity. 1-Lithio-1-methylsulfanylallene (**IId**) is obtained by treatment of 1-methylsulfanyl-1-propyne with butyllithium at –30 to 0°C. Deprotonation of 2-butyne occurs at –30 to 30°C (~15–30 min), formally yielding acetylene ($MeC{\equiv}CCH_2Li$) and allene [$H_2C{=}C{=}C(Me)Li$] intermediates which react with electrophiles to give, depending on the electrophile nature, allene or acetylene

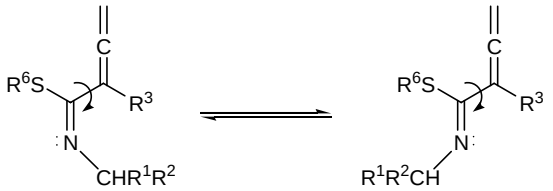
Scheme 1.



R^1, R^2 = H, Alk, $(CH_2)_n$, n = 2–5; R^3 = H, Alk, OAlk, SAlk; R^4, R^5 = H, Alk, $(CH_2)_5$; R^6 = Alk.

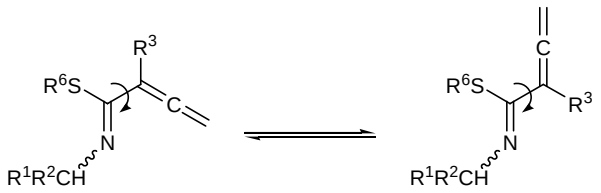
intermediates or their mixture. Lithiated 2-butyne reacts with aliphatic isothiocyanates exclusively in the allene form (**IIe**) [4].

Isothiocyanates take up carbanions following exclusively nucleophilic (carbophilic) mechanism [2, 4]. Unlike other thiocarbonyl compounds [17], formation of thiophilic addition products has not been observed so far. Lithiated allenes **II** react with aliphatic isothiocyanates with heat evolution at low temperature (–100 to –60°C) and at a high rate to afford the corresponding lithium imidothioates **III** in almost quantitative yield. Alkylation of the latter with alkyl iodides or dialkyl sulfates gives 1,3,4-azatrienes **IV** which usually exist as mixtures of *syn* (*Z*) and *anti* (*E*) isomers with respect to the double C=N bond (according to the NMR data) [4].



cis-(*Z*)-**IV** *trans*-(*E*)-**IV**

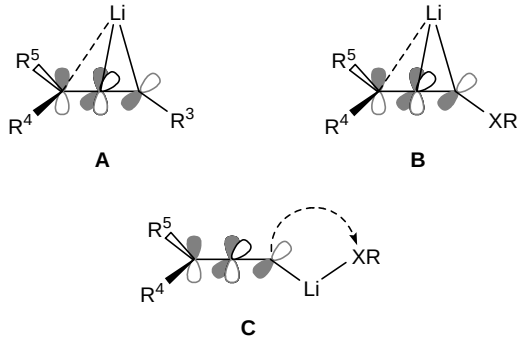
The mechanism of addition of lithiated allenes **II** to isothiocyanates **I** depends on the electron-donor properties of the solvent. Formalistically, the reaction can take purely ionic (two-step) or almost concerted (one-step) channel through four-center transition state like PBC (prereaction bimolecular complex; see Scheme 1). The latter is most likely to be formed in the gas phase or in weakly polar solvents such as THF–hexane system. The regioselectivity at the stage of intramolecular transformations of the kinetically controlled product, 1,3,4-azatriene **IV**, i.e., sigmatropic rearrangements and cyclization, is very sensitive to stereoelectronic parameters of its rotamers arising from restricted rotation about the C–C bond and differing by mutual orientation of the N=C and C=C=C fragments [4].



syn-(*Z*)-**IV** *anti*-(*E*)-**IV**

gauche-**IV**

The calculations showed that the stereoelectronic structure of lithioallenes **II** is governed by the nature of the R^3–R^5 substituents. On the whole, intermediates **II** are pseudochelate structures like **A**–**C** including a three-membered lithium-containing ring (Fig. 1).



If the R^3–R^5 substituents contain no heteroatoms and unsaturated fragments, the site of lithium coordination is determined by spatial accessibility of the carbon center in the cumulene fragment, and the latter deviates from linearity within 15–20 deg. The order of the π-bond interacting with the lithium atom decreases, while the order of the neighboring double bond increases (Fig. 1, structure **IIa**, $R^3 = R^4 = R^5 = H$). The MP2(FU)/6-31G* calculations performed in [18] showed an analogous structural reorganization of the allene fragment in going to deprotonated allene and then to lithioallene. If one of the substituents is linked to the allene fragment through a heteroatom (X = NR, O, S), acceptor power of the corresponding carbon center increases, and the lithium atom is displaced toward that center (structure **B**); In this case, structural reorganization of the allene fragment is similar to that occurring in intermediate **A** [Fig. 1, 1-lithio-1-methylsulfanylallene (**IId**, R^3 = SMe, $R^4 = R^5 = H$)]. Finally, when the substituent contains a heteroatom which is not attached directly to the allene fragment (structure like **C**) or two heteroatoms, one of which is not linked to the allene fragment, the degree of association of the lithium atom decreases giving rise to a pseudochelate ring [Fig. 1, 1-lithio-1-(1-ethoxyethoxy)allene (**IIc**), R^3 = OCH(Me)OEt, $R^4 = R^5 = H$)]. In the latter case, distortion of the allene fragment is minimal. While studying reactions of lithium ion with alkyl-substituted ethenes in terms of the density functional theory (DFT, B3LYP/6-31G*), Froudakis and Stratakis [19] revealed preferential formation of chelate structures analogous to **A**–**C**. These data indicate that interaction of lithioallenes **II** with electron-acceptor solvate shell should not lead to substantial conformational

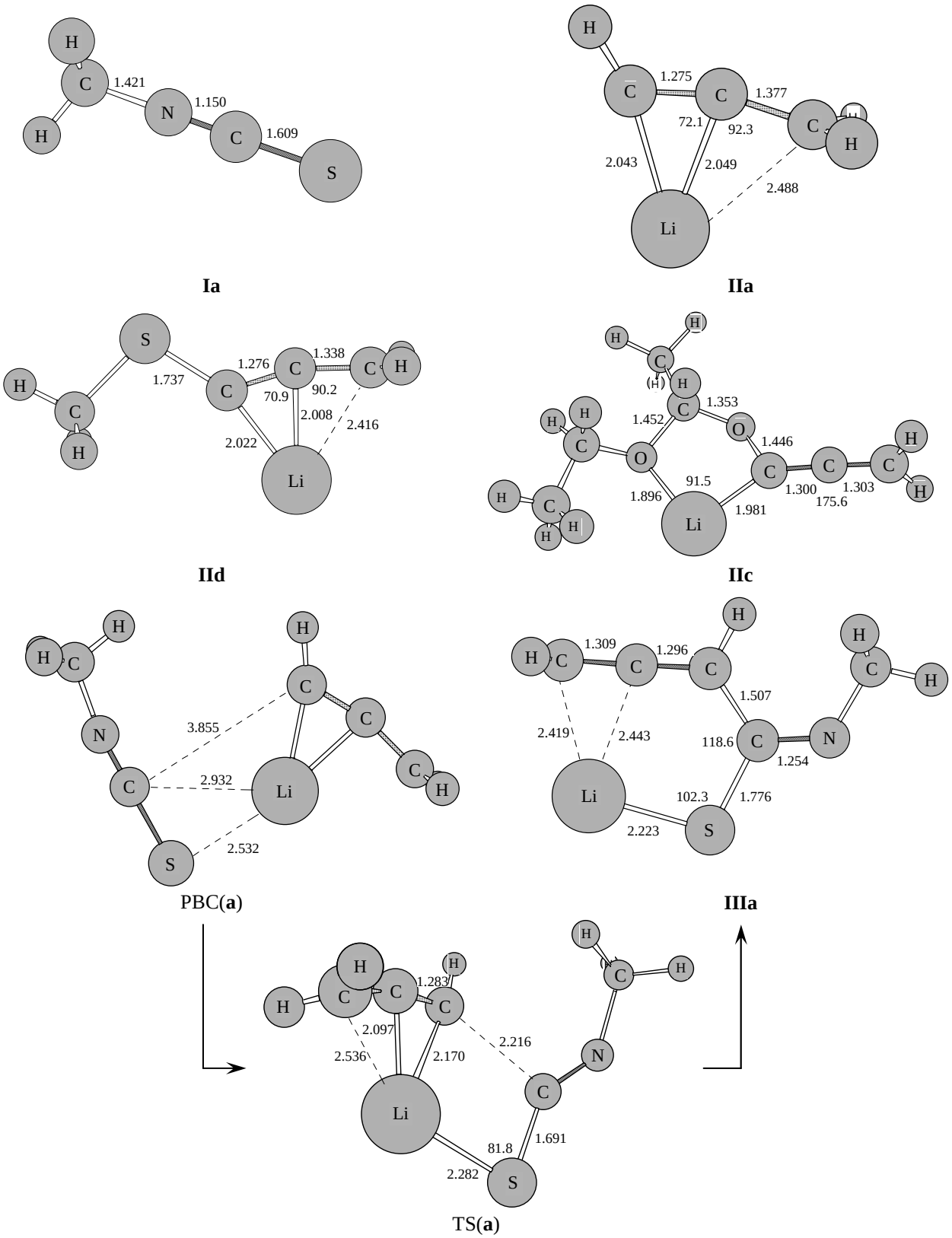


Fig. 1. Molecular structures and principal geometric parameters of initial compounds **Ia**, **IIa**, **IIc**, and **IId**, bimolecular complex PBC (**a**), product **IIIa**, and the corresponding transition state TS(**a**) according to the HF/6-31G** calculations. Here and in Figs. 2–4, bond lengths are given in Å, and bond angles, in deg.

Table 1. Total energies (E_{tot}, a.u.),[a] relative energies (ΔE, kJ/mol), numbers of negative Hessian eigenvalues (λ), zero-point harmonic vibration energies (ZPE, a.u.), imaginary (or least) harmonic frequencies [(iw/w_1), cm^{-1}], and electric dipole moments (μ, D) of structures **Ia**, **IIa**, **IIc**, and **IId**, bimolecular complexes PBC (**a**, **c**, **d**), products **IIIa**, **IIIc**, and **IIId**, and transition states TS (**a**, **c**, **d**), calculated by the HF/6-311G** and B3LYP/6-31G** (in parentheses) methods

Structure	E_{tot}	ΔE	λ	ZPE	iw/w_1	μ
Ia	–529.43538 (–530.95277)		0 (0)	0.05171 (0.04779)	107 (148)	5.21 (4.29)
IIa	–122.72782 (–123.58891)		0 (0)	0.04794 (0.04541)	201 (255)	3.78 (3.41)
PBC(**a**)	–652.18424 (–654.57937)	69.6 (57.4)	0 (0)	0.10096 (0.09431)	23 (31)	5.85 (3.89)
TS(**a**)	–652.15538 (–654.55069)	144.0 (132.7)	1 (1)	0.10146 (0.09497)	*i*367 (*i*412)	2.99 (2.36)
IIIa	–652.21079 (–654.60127)	0.0 (0.0)	0 (0)	0.10564 (0.09789)	41 (55)	8.47 (7.53)
IIc	–428.58688 (–431.28531)		0 (0)	0.18000 (0.16786)	38 (43)	7.62 (6.78)
PBC(**c**)	–958.04923 (–962.26102)	137.2 (117.8)	0 (0)	0.19327 (0.18713)	40 (51)	3.11 (2.86)
TS(**c**)	–958.01843 (–962.23117)	218.0 (196.1)	1 (1)	0.19387 (0.18809)	*i*854 (*i*937)	2.06 (1.84)
IIIc	–958.10154 (–962.30593)	0.0 (0.0)	0 (0)	0.19584 (0.18921)	68 (77)	3.43 (3.05)
IId	–559.28263 (–561.10205)		0 (0)	0.08058 (0.07560)	89 (91)	5.60 (5.08)
PBC(**d**)	–1088.74278 (–1092.07989)	103.1 (102.4)	0 (0)	0.13349 (0.12480)	17 20	3.99 (3.29)
TS(**d**)	–1088.71311 (–1092.05007)	180.9 (180.6)	1 (1)	0.13453 (0.12516)	*i*576 (*i*617)	2.21 (1.97)
IIId	–1088.78209 (–1092.11893)	0.0 (0.0)	0 (0)	0.13667 (0.12692)	25 (34)	7.78 (7.16)

[a] 1 a.u. = 2622.9897 kJ/mol.

reorganization up to formation of solvent-separated ion pair.

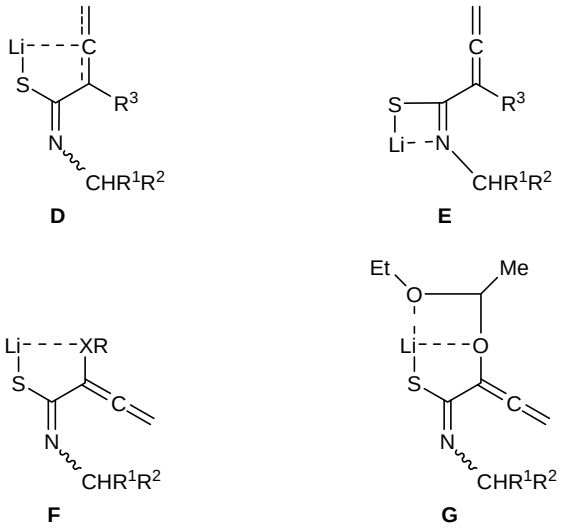
The formation of a prereaction bimolecular complex (PBC) between methyl isothiocyanate (**Ia**) and lithioallene (**IIa**) (Fig. 1, structure PBC, $R^1 = R^2 = R^3 = R^4 = R^5 = H$) is characterized by a considerable gain in the total energy relative to the isolated molecules. The heat of complex formation with no zero-point vibration energy (ZPE) taken into account is 55.2 (HF) and 98.9 kJ/mol (B3LYP). Introduction of corrections for ZPE slightly reduces these values, by 3.1 and 2.9 kJ/mol, respectively. The structure of PBC is planar with respect to heavy atoms, the coordination number of the lithium atom increases, and the degree of its association also rises. According to the HF and B3LYP calculations, the heat of addition (i.e., of the transformation of PBC into adduct **IIIa**) is 69.6 and 57.4 kJ/mol, respectively (Table 1, Fig. 1). Analysis of the PES shows that in the first stage the main component of the reaction coordinate is the interatomic distance Li···S=C; subsequently, this parameter becomes the distance $C_{thione}\cdots C_{allene}$. The reaction includes a single step: no stable intermediates were found along the gradient line connecting the stationary states PBC and **IIIa**. Transition state TS(**a**) is a four-center structure which implies almost concerted mechanism of the addition. The energy of activation of this process is 74.4 (HF) and 75.3 kJ/mol (B3LYP). With account taken of ZPE, the difference in the thermodynamic stability decreases by 12.3 (HF) and 9.4 kJ/mol (B3LYP), and the energy of activation insignificantly increases (by 1.3 and 1.7 kJ/mol,

respectively, for HF and B3LYP models; Table 1). Judging by the dipole moments of molecular systems corresponding to critical points on the PES (Table 1), transition from the gas phase to a polar solvent should be accompanied by additional stabilization of the products and some increase in the energy of activation for the transformation of PBC into adduct **IIIa**.

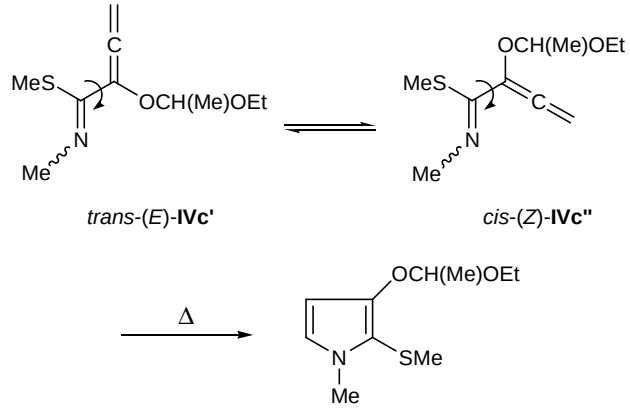
On a qualitative level, the topology of the PES for the addition of methyl isothiocyanate (**Ia**) to α-lithiated 1-(1-ethoxyethoxy)allene (**IIc**) and methylsulfanylallene **IId** is analogous to that found for the transformation of PBC into **IIIa**. The reactions occur in one step, and their transition states are four-center structures with a lesser degree of charge separation, as compared to TS(**a**). The heats of the reactions PBC(**c**) → adduct **IIIc** [R^3 = OCH(Me)OEt, R^1 = R^2 = R^4 = R^5 = H] and PBC(**d**) → **IIId** [R^3 = SMe, R^1 = R^2 = R^4 = R^5 = H] increase and attain, respectively, 137.2 and 103.1 kJ/mol (HF) and 117.8 and 102.4 kJ/mol (B3LYP). The energies of activation are less sensitive to the R^3 substituent, and they approach those typical of the reaction PBC(**a**) → **IIIa** [78.2 and 77.8 kJ/mol (HF); 78.3 and 80.8 kJ/mol (B3LYP)]. Corrections for ZPE lead to qualitatively similar variations (Table 1).

Like lithioallenes **II**, the conformational states of lithium imidothioate **III** are determined by the degree of competing coordination of the lithium atom at the cumulene fragment (**D**), lone electron pair on the nitrogen atom (**E**), and unsaturated fragments or heteroatoms in the R^3 substituent (if they are present; structures **F** and **G**). As a rule, predominant coordination of the lithium atom at the allene fragment (**D**) or nitrogen atom (**E**), stabilizes *trans* conformation of adduct **III** which is capable of retaining its configuration after delithiation (alkylation). Favorable coordination of the lithium atom at the R^3 substituent [R^3 = XR (NR_2, OR, SR); structures **F** and **G**] stabilizes mainly the *cis* conformer. The conformers are quite stable. The energy of activation for their interconversion exceeds 40 kJ/mol. Lithium imidothioate **IIIc** (Fig. 2), whose R^3 substituent contains two heteroatoms [R^3 = OCH(Me)OEt, R^1 = R^2 = R^4 = R^5 = H], gives rise to three deep stationary states **IIIc'**–**IIIc'''** differing by the mode of lithium coordination. The energies of activation for the transformations of **IIIc''** into **IIIc'** (**D** → **E**) and of **IIIc''** into **IIIc'''** (**D** → **G**) are, respectively, 44.4 and 87.6 kJ/mol (HF calculations). The thermodynamic stability of the stationary state increases as the degree of association of the lithium atom rises (Table 2). The most stable is structure **IIIc'''** due to formation of an additional coordination bond, despite negative dipole–dipole interactions (**G**, R^1 = R^2 = H). The difference in the thermodynamic stability of conformers **IIIc'** and **IIIc''** (82.3 kJ/mol, Table 2), may be assumed to be the lower value of the coordination bond energy. After delithiation with methyl iodide, structures **IIIc'** and **IIIc''** slide down to a single skewed *trans*-1,3,4-azatriene structure **IVc'**, while **IIIc'''** is converted into skewed *cis*-1,3,4-azatriene **IVc''**. As a result, the relative stabilities are inversed so that the most stable is the least polar structure **IVc'** (Fig. 2, Table 2). Conformational states **IVc'** and **IVc''** become less rigid, the energy of activation for their interconversion appreciably decreases (as compared to the corresponding transformations in **IIIc**), and the energy of activation for the transformation *cis*-**IVc''** → *trans*-**IVc'** is 26.1 kJ/mol (HF) (Scheme 2).

Presumably, the high rotational mobility of 1,3,4-azatriene **IVc** is the main factor responsible for its



Scheme 2.



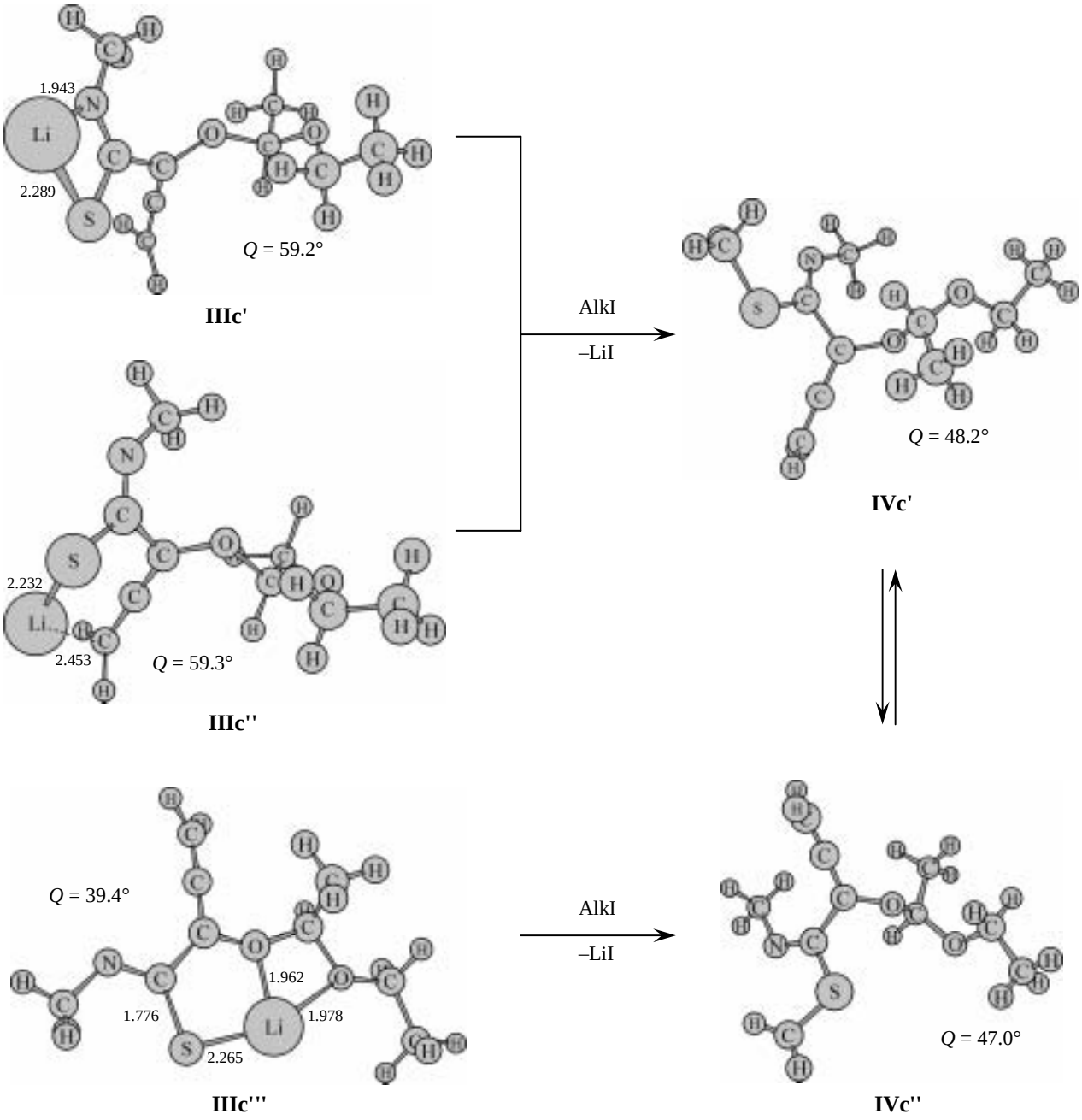
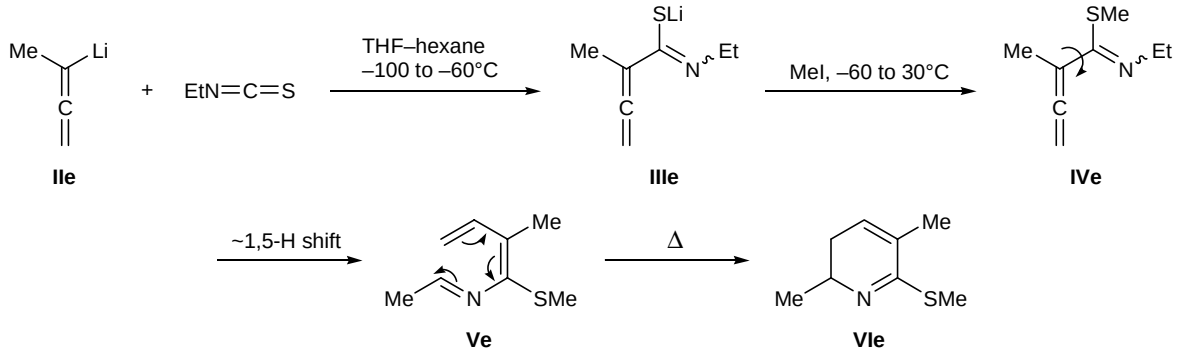


Fig. 2. Molecular structures of the most stable conformers of imidothioate **IIIc** and 1,3,4-azatriene **IVc** according to the HF/6-311G** calculations; *Q* is the angle between the C=N bond and the plane formed by the bonds at the α-carbon atom of the allene fragment.

facile intramolecular rearrangement with formation of a pyrrole ring (together with dihydropyridine) [4]. According to the calculations, rotation about the C–C bond in *cis* conformer **IVc''**, leading to enhanced interaction between π orbitals of the terminal carbon atom in the allene fragment and nitrogen atom (which results in formation of σ-C–N bond), is characterized by a low activation barrier (107.4 kJ/mol, HF).

Unlike 1-lithio-1-(1-ethoxyethoxy)allene (**IIc**) [4], reactions of lithiated 2-butyne (**IIe**) with aliphatic isothiocyanates yield exclusively 2,3-dihydropyridines [13]. No corresponding pyrrole derivatives were detected among products of thermally induced reactions (Scheme 3). The calculations showed that 1,3,4-azatriene **IVe** formed by methylation of the 1-lithio-1-methylallene adduct with ethyl isothiocyanate (**IIIe**)

Scheme 3.



(Fig. 3) can exist as *cis* and *trans* rotamers which reproduce the configuration of the lithiated analogs. The *cis* rotamer is more stable than the *trans* structure by 13.7 kJ/mol (Table 2). The depth of the potential minima corresponding to the above rotamers is very small. The barriers to their transitions into enantiomeric plane-chiral *gauche* conformer **IVe** (Fig. 3) are 6.2 and 4.3 kJ/mol (HF) for the *cis* and *trans* rotamers, respectively. As a result of rotational transition, the thermodynamic stability of the chiral product increases by 17.7 kJ/mol relative to the *cis* structure (HF). The allene fragment in the *gauche* conformer of 1,3,4-azatriene **IVe** becomes almost orthogonal to the imidothioate fragment N=C–S(Me) (Q = 95.2°).

As shown in [13], 1,3,4-azatriene **IVe** is capable of undergoing thermally induced isomerization into stable 1,3,5-azatriene **Ve** and then into 2,3-dihydropyridine **VIe** (Fig. 3). From the viewpoint of stereochemistry, 1,5-hydride shift initiating the conversion of **IVe** into **Ve** is most favorable for the *cis* conformer of **IVe**.

Table 2. Total energies (E_{tot}, a.u.),[a] relative energies (ΔE, kJ/mol), numbers of negative Hessian eigenvalues (λ), zero-point harmonic vibration energies (ZPE, a.u.), imaginary (or least) harmonic frequencies [(iw/w_1), cm^{-1}], and electric dipole moments (μ, D) of structures **IIIc**, **IVc**, **IVe**–**VIe**, and **Vf**–**VIIf** and transition states TS(**e**1), TS(**e**2), TS(**f**1), and TS(**f**2), calculated by the HF/6-311G** method

Structure	E_{tot}	ΔE	λ	ZPE	iw/w_1	μ
IIIc'	–958.09193	25.2	0	0.23740	22	3.43
IIIc''	–958.06055	107.5	0	0.23667	27	8.55
IIIc'''	–958.10154	0.0	0	0.23747	30	9.78
IVc'-*trans*	–990.18235	0.0	0	0.27624	19	1.78
IVc'-*cis*	–990.18000	6.2	0	0.27607	17	2.89
IVe-*cis*	–762.40939	173.0	0	0.20535	87	1.82
IVe-*trans*	–762.40418	186.7	0	0.20541	94	1.41
IVe-*gauche*	–762.41616	155.3	0	0.20523	19	1.49
TS(**e**1)	–762.34163	350.8	1	0.20980	*i*1854	1.60
Ve	–762.43495	106.0	0	0.20549	63	1.69
TS(**e**2)	–762.32684	389.6	1	0.21079	*i*1463	1.79
VIe	–762.47537	0.0	0	0.20546	36	1.64
Vf'	–1031.30148	103.8	0	0.34182	29	2.48
Vf''	–1031.29641	117.1	0	0.34176	31	2.50
TS(**f**1)	–1031.23419	280.3	1	0.34701	*i*1276	4.11
VIf	–1031.34107	0.0	0	0.34599	43	2.44
VIIf	–1031.34101	0.1	0	0.34587	41	1.84
TS(**f**2)	–1031.24707	246.5	1	0.34571	*i*1164	4.67

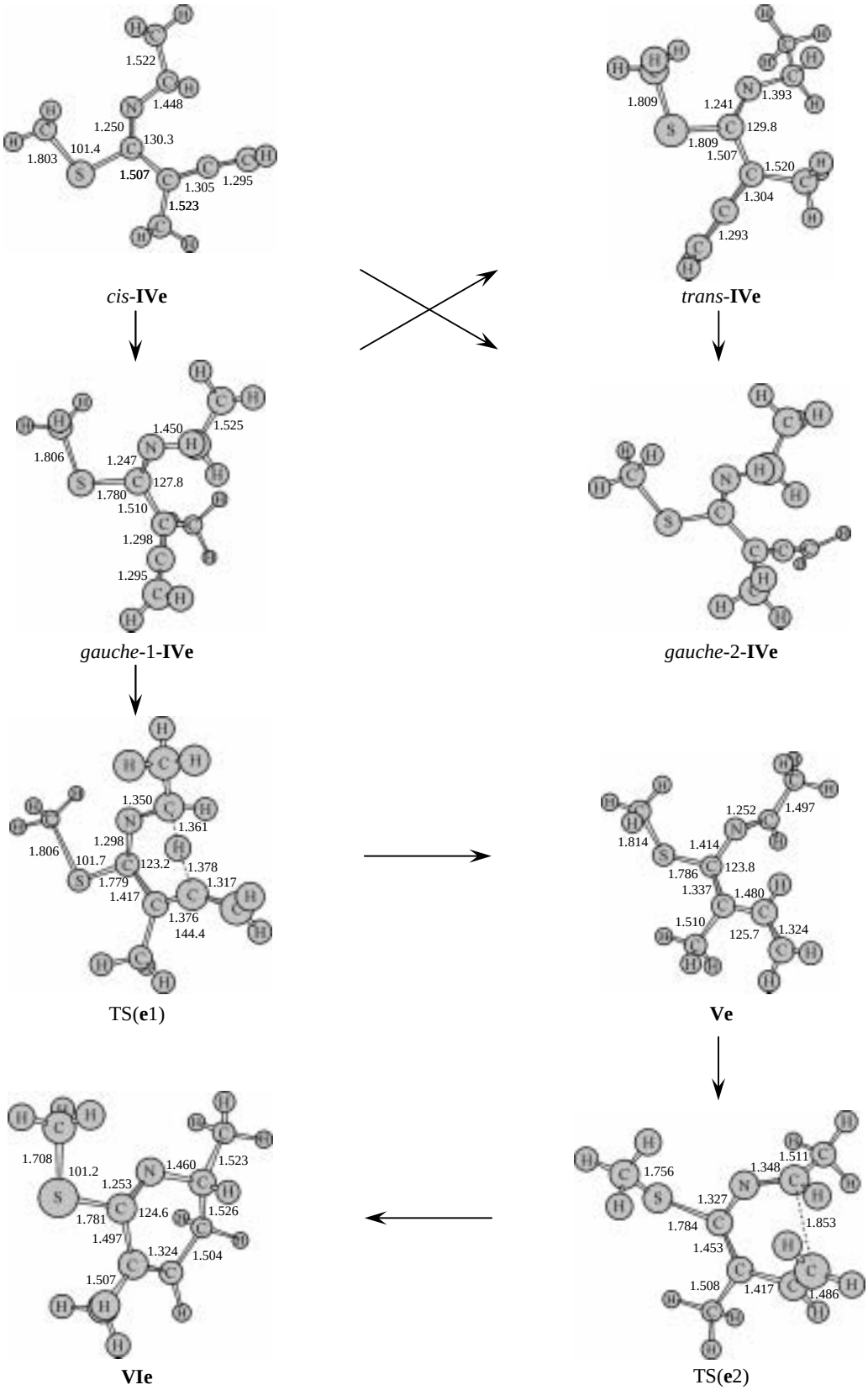
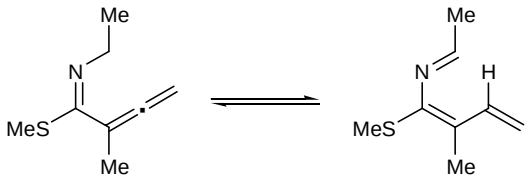


Fig. 3. Molecular structures and principal geometric parameters of compounds **IVe**, **Ve**, and **VIe** and the corresponding transition states TS(**e**1) and TS(**e**2) according to the HF/6-31G** calculations.

However, the contribution of that sigmatropic rearrangement is insignificant because of the short lifetime of *cis*-**IVe**. Probably, the major initial state is *gauche*-**IVe**; the heat of its transformation into isomer **Ve** is 49.3 kJ/mol (Table 2).



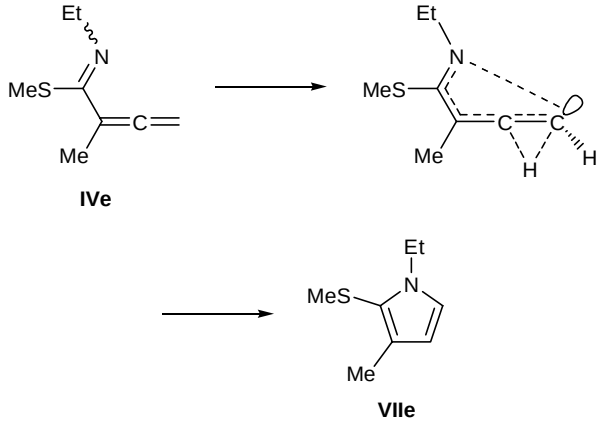
IVe **Ve**

The structure of transition state TS(**e**1) arising upon moving along the gradient line connecting *gauche*-**IVe** and **Ve** suggests that structural reorganization accompanying the sigmatropic rearrangement includes mainly flattening of the molecular skeleton (Q = 8.7°) which tends to adopt *cis* configuration with bridging position of the migrating hydrogen (Fig. 3). The energy of activation for this transition is 195.5 kJ/mol (Table 2).

Thermal cyclization of **Ve** into dihydropyridine **VIe** is more exothermic than the sigmatropic rearrangement of 1,3,4-azatriene **IVe** into 1,3,5-azatriene **Ve**. The gain in the thermodynamic stability of dihydropyridine **VIe** relative to 1,3,5-azatriene **Ve** is 106.0 kJ/mol (Table 2). However, the energy of activation for the cyclization process exceeds by a factor of almost 1.5 that found for the isomerization of 1,3,4-azatriene **IVe** into 1,3,5-azatriene **Ve** and is 283.6 kJ/mol. The dynamics of structural reorganization during the conversion of **Ve** into **VIe** includes initial rotation of the terminal vinyl fragment and the subsequent disrotatory cyclization at the unsaturated N=C bond. Introduction of corrections for ZPE (within 0.7 kJ/mol) does not affect the relative stabilities of **IVe**, **Ve**, and **VIe**. By contrast, corrections for ZPE strongly influence the kinetic parameters of the transitions **IVe** → **Ve** and **Ve** → **VIe**: The energies of transition states TS(**e**1) and TS(**e**2) are reduced by 12.0 and 13.9 kJ/mol, respectively. In the course of intramolecular transformations, the polarity of molecular systems changes only slightly ($\Delta\mu$ < 0.4 D); therefore, variation of the solvent polarity could not lead to appreciable variation of the thermodynamic and kinetic parameters of the process.

In order to estimate the probability for formation of five-membered heterocycles from 1,3,4-azatrienes and 1,3,5-azatrienes, we performed quantum-chemical analysis of the potential energy surfaces for intramolecular rearrangemens of 1,3,4-azatriene **IVe** and 1,3,5-azatriene **Ve** into pyrrole **VIIe**. Theoretically possible formation of a pyrrole ring, e.g., via 1,2-hydride shift in the *cis* isomer of 1,3,4-azatriene **IVe**, requires a considerably higher energy as compared to the rearrangement into 1,3,5-azatriene **Ve** (437.1 kJ/mol, HF). This is confirmed experimentally: no formation of pyrroles in thermally induced transformations of 1,3,4-azatrienes like **IVe** with various substituents on the nitrogen atom was observed so far [4]. According to the calculations, the rearrangement of 1,3,5-azatriene **Ve** into pyrrole **VIIe**, initiated by 1,6-hydride shift (Scheme 4), is characterized by a high activation barrier (394.6 kJ/mol, HF) due to unfavorable steric conditions, which is also consistent with the experimental data [4].

Scheme 4.

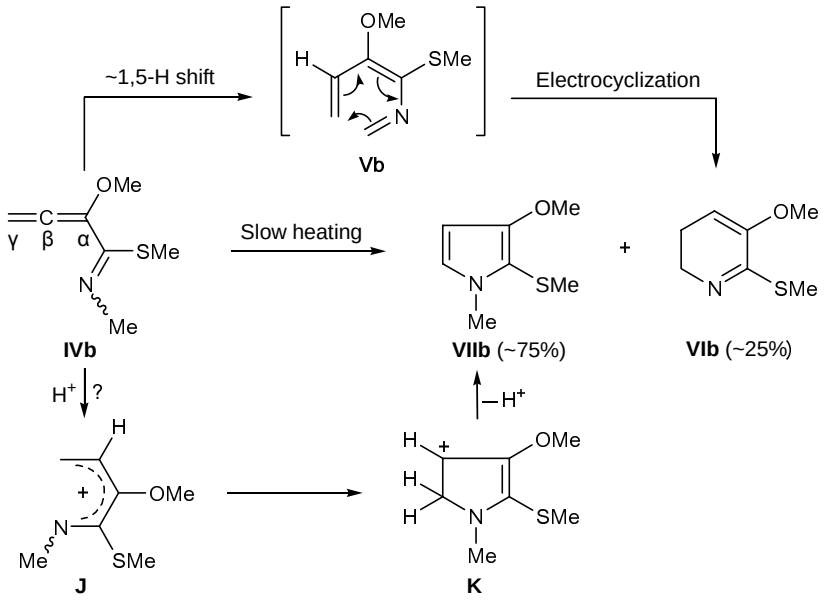


IVe **VIIe**

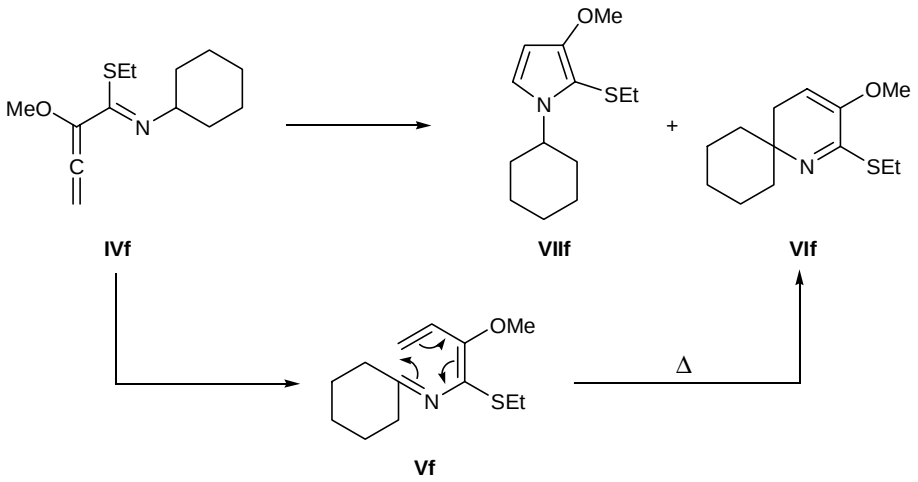
Apart from the reactions of isothiocyanates with 1-lithio-1-(1-ethoxyethoxy)allene (**IIc**) [4], concurrent thermally induced intramolecular rearrangements of 1,3,4-azatrienes **IV** were also observed in the reactions of lithiated methoxyallene **IIb** with alkyl and cycloalkyl isothiocyanates [4, 8–10].

In an early publication on the reaction of 1-lithio-1-methoxyallene (**IIb**) with methyl isothiocyanate, leading to a ~1:3 mixture of 2,3-dihydropyridine **VIb** and pyrrole **VIIb**, it was presumed that the formation of pyrrole ring involves protonated form of 1,3,4-azatriene **IVb** [8]. Here, the most favorable for cyclization is attack by proton on the π orbital localized on the C_β–C_γ-centers, which activates *p* orbital on the γ-carbon atom and promotes its interaction with the nitrogen π orbital. The calculated energies of activation for the 1,5-H shift (**IVb** → **Vb**) and the subsequent electrocyclic rearrangement of 1,3,5-azatriene **Vb** into dihydropyridine **VIb** are 114.3 and 90.1 kJ/mol,

Scheme 5.



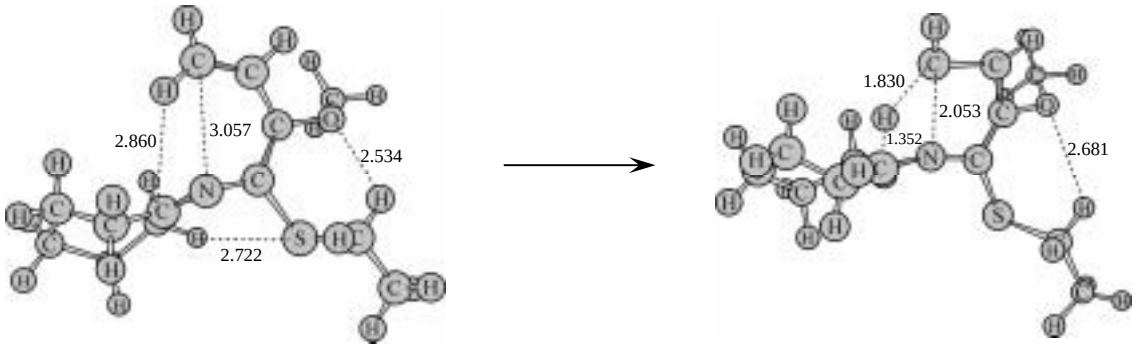
Scheme 6.



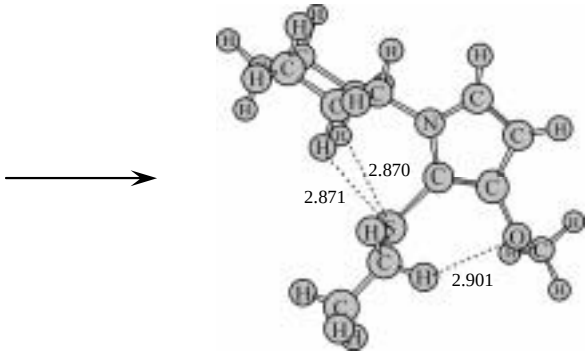
respectively, whereas the formation of pyrrole ring (**VIIb**) through protonated structures like **J** and **K** is characterized by an activation barrier of 44.9 kJ/mol (HF) (Scheme 5).

N-Cyclohexyl-1-ethylsulfanyl-2-methoxy-2,3-butadien-1-imine (**IVf**) obtained by reaction of 1-lithio-1-methoxyallene (**IIb**) with cyclohexyl isothiocyanate, followed by alkylation of the adduct with ethyl iodide [9], behaves similarly to compound **IVb**. Thermally initiated transformation of azatriene **IVf** also yields a mixture of 2,3-dihydropyridine **VIf** and pyrrole **VIIf** but at a different ratio (~9:1) (Scheme 6).

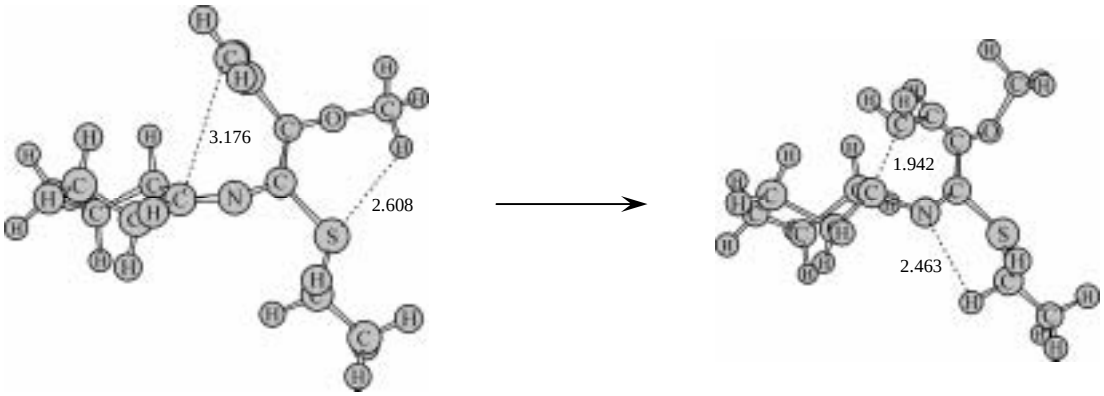
According to the calculations, the transformation of intermediate **IVf** into stable isomer **Vf** occurs in one step via 1,5-hydrogen migration and flattening of the molecular skeleton. The process is analogous to the transformation of 1,3,4-azatriene **IVe** into 1,3,5-azatriene **Ve**. Its energy of activation is lower, 141.9 kJ/mol (HF). Electrocyclic rearrangement of 1,3,5-azatriene **Vf** into dihydropyridine **VIf** can formally compete with the transformation into pyrrole **VIIf** (e.g., via 1,6-hydride shift). The probability for the rearrangements to occur in the first step is determined by favorableness of steric conditions for the most stable rotamers of compound **Vf** [9]. On the potential energy surface for rotational transformation we revealed two deepest minima corresponding to rotamers **Vf'** and **Vf''**, the latter being slightly more stable (Table 2, Fig. 4). The main stereoelectronic difference in these



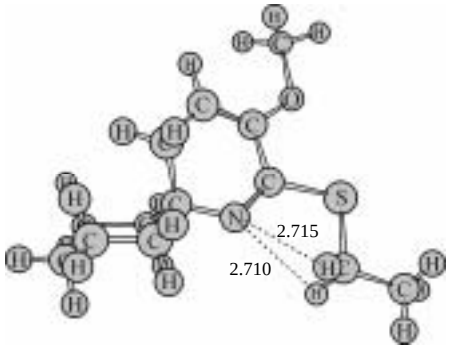
Vf' TC(**f**1)



VIIf



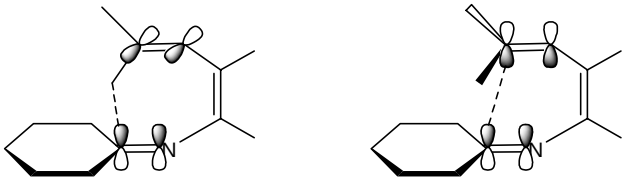
Vf'' TC(**f**2)



Vf

Fig. 4. Molecular structures of 1,3,5-azatriene conformers **Vf'** and **Vf''**, intramolecular transformation products **VIf** and **VIIf,** and transition states TS(**f**1) and TS(**f**2).

states is mutual orientation of the π systems of the vinyl and imine fragment. In structure **Vf'**, they are arranged sandwich-like with respect to the six-membered ring and are orthogonal, while their arrangement in **Vf''** is closer to coplanar.



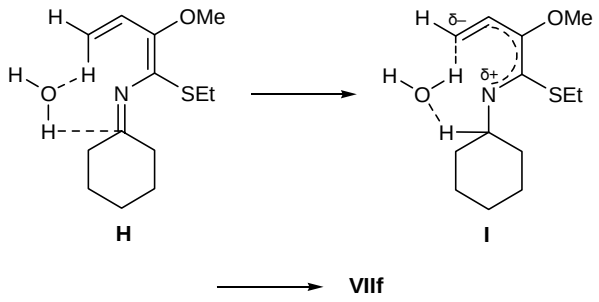
Vf' **Vf''**

There are now vast experimental data [4] indicating that precursors of pyrroles are 1,3,4-azatrienes **IV**. Nevertheless, we believed it necessary to perform quantitative estimation of two more possible channels for pyrrole ring formation (through 1,3,5-azatrienes **V**). One of these has already been considered above using *N*-ethylidene-2-methyl-1-methylsulfanyl-1,3-butadien-1-amine (**Ve**) as an example. However, unlike azatriene **Ve** whose thermal cyclization yields exclusively the corresponding dihydropyridine, intramolecular transformations of azatriene **IVf** (apart from the isomerization into azatriene **Vf**) result in formation of a mixture of dihydropyridine **VIf** and pyrrole **VIIf**. Therefore, it was important to find out whether replacement of the methyl group in **Ve** by methoxy affects to an appreciable extent thermodynamic parameters of the transformation **Vf** → **VIIf**, making it energetically favorable or at least feasible.

The calculations showed that the relative stabilities of dihydropyridine **VIf** and pyrrole **VIIf** are almost similar (Table 2). The cyclization of 1,3,5-azatriene **Vf''** to dihydropyridine **VIf** is by 13.4 kJ/mol more exothermic than the transformation of azatriene **Vf'** into **VIIf**; the calculated heat of the former reaction is 117.1 kJ/mol (HF). The rearrangement of conformer **Vf'** into pyrrole **VIIf**, initiated by 1,6-hydride shift (Fig. 4), can occur as follows. The β-vinyl proton reacts with the carbon π orbital in the six-membered ring; the *p* orbital thus released interacts with the antibonding π orbital on the nitrogen atom, giving rise to σ bond between the β-vinyl carbon atom and nitrogen. The vinyl π orbital and lone electron pair on the nitrogen atom are not involved in the rearrangement. The energy of activation of this process is 176.5 kJ/mol (HF) (Table 2), i.e., it is more than twice as low as the barrier to the transformation of 1,3,5-azatriene **Ve** into pyrrole **VIIe** (394.6 kJ/mol, HF).

The electrocyclic rearrangement **Vf''** → **VIf** (see Table 2 and Fig. 4) requires a lower activation energy (129.4 kJ/mol, HF). Introduction of corrections for ZPE almost does not affect the relative thermodynamic stability of the initial compounds and products, while the energy of activation decreases by 10–13 kJ/mol. Thus, despite more favorable relation between the thermodynamic parameters for the reaction **Vf'** → **VIIf**, as compared to **Vf''** → **VIf**, and greater population of rotamer **Vf'**, as compared to **Vf''**, the reaction equilibrium is displaced toward dihydropyridine **VIf** due to more favorable kinetic parameters of the rearrangement **Vf''** → **VIf**. 1,3,5-Azatriene **Vf** does not give rise to stable rotamers like **Vf'**; presumably, this is the reason why no pyrrole products are formed in the thermally induced reaction [11].

In going to protic solvents, the activation barrier to the cyclization of 1,3,5-azatriene **Vf'** into pyrrole **VIIf**, promoted by external proton-donor species, may be reduced as a result of concerted intermolecular proton transfer. Analysis of the model reaction **Vf'** → **VIIf** with participation of water as mediator gives a lower energy of activation by a factor of about 1.5 (132.1 kJ/mol, HF), and this rearrangement becomes equally probable to the rearrangement **Vf''** → **VIf**.



H **I** **VIIf**

Structure **I** is an unstable intermediate which undergoes cyclization to pyrrole structure with an activation energy of less than 4 kJ/mol. However, no experimental proofs for such a facile transformation of 1,3,5-azatriene **Vf'** into pyrrole **VIIf** have been obtained so far. The above considered channel of intramolecular rearrangement (with compound **IVb** as an example), leading to pyrrole ring closure via protonation of the β-carbon atom in the allene fragment of **IV** seems to be even more preferred. However, it was not confirmed experimentally as well. The energy of activation for the formation of pyrrole ring from protonated form of **IVf** is 67.2 kJ/mol (HF). The probability for formation of protonated species in media containing active hydroxonium ions depends on

the substituent in the allene fragment. The presence of a heteroatom directly attached to the α- or γ-carbon center enhances the affinity of the β-carbon atom for proton and hence increases the probability for its protonation. Presumably, just that factor is responsible for the formation of pyrroles together with dihydropyridines in reactions of lithiated alkoxyallenes with isothiocyanates [8].

Thus, 1,3,4-azatrienes **IV** formed by addition of lithiated allenes to isothiocyanates are transformed into more stable 1,3,5-azatriene isomers **V** which undergo ring closure to give mainly dihydropyridines. Provided that there are conditions for formation of protonated 1,3,4-azatriene, concurrent cyclization to pyrrole derivatives becomes possible.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 01-03-32698a).

REFERENCES

1. Dmitrieva, L.L., Nikitina, L.P., Albanov, A.I., Sarapulova, G.I., Nedolya, N.A., and Brandsma, L., *Russ. J. Org. Chem.*, 2004, vol. 40, p. 178.
2. Walter, W. and Bode, K.-D., *Angew. Chem.*, 1966, vol. 78, p. 39; Petrov, K.A. and Andreev, L.N., *Usp. Khim.*, 1969, vol. 38, p. 41; Wakefield, B.J., *The Chemistry of Organolithium Compounds*, Oxford: Pergamon, 1974, pp. 128, 219; Drobnica, L., Kristian, P., and Augustin, J., *The Chemistry of Cyanates and Their Thio Derivatives*, Patai, S., Ed., Chichester: Wiley, 1977, part 2, chap. 22, p. 1003; *Comprehensive Organic Chemistry*, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1979, vol. 2. Translated under the title *Obshchaya organicheskaya khimiya*, Moscow: Khimiya, 1982, vol. 3, p. 629; Brandsma, L. and Verkruijsse, H., *Preparative Polar Organometallic Chemistry*, Berlin: Springer, 1987, vol. 1, pp. 34, 35, 152, 190, 219, 221, 224, 226, 233; Wakefield, B.J., *Best Synthetic Methods. Organolithium Methods*, London: Academic, 1988, pp. 96, 102; Brandsma, L., *Studies in Organic Chemistry. 34. Preparative Acetylenic Chemistry*, Amsterdam: Elsevier, 1988, pp. 100, 108, 299; Brandsma, L., *Preparative Polar Organometallic Chemistry*, Berlin: Springer, 1990, vol. 2, pp. 9, 30, 32, 35, 36, 73; Nedolya, N.A., Trofimov, B.A., and Senning, A., *Sulfur Rep.*, 1996, vol. 17, p. 183; Crossley, R. and Shepherd, R.G., *J. Chem. Soc., Perkin Trans. 1*, 1985, p. 1917; Jagodzinski, T.S., Dziembowska, T.M., and Szczodrowska, B., *Bull. Soc. Chim. Belg.*, 1989, vol. 98, p. 327.
3. *Comprehensive Organic Chemistry*, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1979, vol. 4. Translated under the title *Obshchaya organicheskaya khimiya*, Moscow: Khimiya, 1984, vol. 7, p. 21.
4. Nedolya, N.A., *PhD Thesis of Utrecht University*, Utrecht (The Netherlands), 1999; Brandsma, L., *Eur. J. Org. Chem.*, 2001, p. 4569.
5. Brandsma, L., Nedolya, N.A., Verkruijsse, H.D., Owen, N.L., Li Du, and Trofimov, B.A., *Tetrahedron Lett.*, 1997, vol. 38, p. 6905.
6. Brandsma, L., Nedolya, N.A., Van der Kerk, A.S.H.T.M., Heerma, V., Lutz, E.T.H.G., de Lang, R.-J., Afonin, A.V., and Trofimov, B.A., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1997, p. 865; Brandsma, L., Nedolya, N.A., Heerma, V., Van der Kerk, A.S.H.T.M., Lutz, E.T.H.G., de Lang, R.-J., Afonin, A.V., and Trofimov, B.A., *Khim. Geterotsikl. Soedin.*, 1997, p. 572; Nedolya, N.A., Brandsma, L., and Trofimov, B.A., *Khim. Geterotsikl. Soedin.*, 2002, p. 1396.
7. Brandsma, L., Nedolya, N.A., de Lang, R.-J., and Trofimov, B.A., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1996, p. 3024.
8. Nedolya, N.A., Brandsma, L., and Trofimov, B.A., *Zh. Obshch. Khim.*, 1996, vol. 66, p. 2042.
9. Nedolya, N.A., Brandsma, L., and Trofimov, B.A., *Khim. Geterotsikl. Soedin.*, 1996, p. 917.
10. Nedolya, N.A., Brandsma, L., de Lang, R.-J., and Trofimov, B.A., *Russ. J. Org. Chem.*, 1997, vol. 33, p. 76; Nedolya, N.A., Brandsma, L., Zinov'eva, V.P., and Trofimov, B.A., *Russ. J. Org. Chem.*, 1997, vol. 33, p. 80; Nedolya, N.A., Brandsma, L., Tarasova, O.A., Verkruijsse, H.D., and Trofimov, B.A., *Tetrahedron Lett.*, 1998, vol. 39, p. 2409.
11. Brandsma, L., Nedolya, N.A., Tarasova, O.A., Klyba, L.V., Sinegovskaya, L.M., and Trofimov, B.A., *Russ. J. Org. Chem.*, 1999, vol. 35, p. 928.
12. Nedolya, N.A., Brandsma, L., Shlyakhtina, N.I., and Fedorov, S.V., *Khim. Geterotsikl. Soedin.*, 2002, p. 707; Nedolya, N.A., Brandsma, L., Shlyakhtina, N.I., Fedorov, S.V., and Klyba, L.V., *Russ. J. Org. Chem.*, 2002, vol. 38, p. 917; Nedolya, N.A., Schlyakhtina, N.I., Klyba, L.V., Ushakov, I.A., Fedorov, S.V., and Brandsma, L., *Tetrahedron Lett.*, 2002, vol. 42, p. 9679.
13. Nedolya, N.A., Brandsma, L., and Trofimov, B.A., *Dokl. Ross. Akad. Nauk*, 1996, vol. 350, p. 68.
14. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, J.A., Jr., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrew-

ski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C., and Pople, J.A., *Gaussian 98, Revision B.03*, Pittsburgh PA; Gaussian, 2003.

15. Minyaev, R.M., *Usp. Khim.*, 1994, vol. 63, p. 933.
16. Brandsma, L. and Verkruijsse, H., *Studies in Organic Chemistry. 8. Synthesis of Acetylenes, Allenes and Cumulenes. A Laboratory Manual*, Amsterdam: Elsevier, 1981; Brandsma, L. and Verkruijsse, H., *Preparative Polar Organometallic Chemistry*, Berlin: Springer, 1987, vol. 1; Epsztein, R., *Studies in Organic Chemistry. 5. Comprehensive Carbanion Chemistry. Part B. Selectivity in Carbon–Carbon Bond Forming Reactions*, Bruncel, E. and Durst, T., Eds., Amsterdam: Elsevier, 1984, p. 107; *Methoden der organische Chemie (Houben–Weyl)*, E 19d; *Organometallics in Synthesis. A Manual*, Schlosser, M., Ed., Chichester: Wiley, 1994.
17. Schönberg, A., Stephenson, A., Kalschmitt, H., Peterson, E., and Schulton, H., *Chem. Ber.*, 1933, vol. 66, p. 237; Beak, P. and Worley, J.W., *J. Am. Chem. Soc.*, 1972, vol. 94, p. 597; Schaumann, E. and Walter, W., *Chem. Ber.*, 1974, vol. 107, p. 3562; Beak, P., Yamomoto, J., and Uptob, C.J., *J. Org. Chem.*, 1975, vol. 40, p. 3052; Paquer, D., *Bull. Soc. Chim. Fr.*, 1975, p. 1439; Ohno, A., Nakamura, K., Uohama, M., and Oka, S., *Chem. Lett.*, 1975, p. 983; Okazaki, R., Fujii, T., and Inamoto, N., *J. Chem. Soc., Chem. Commun.*, 1984, p. 1010; Masson, S., Mothes, V., and Thuillier, A., *Tetrahedron*, 1984, vol. 40, p. 1573; Verkruijsse, H.D. and Brandsma, L., *J. Organomet. Chem.*, 1987, vol. 332, p. 95.
18. Lambert, C., Schleyer, P.v.R., and Würthwein, E.-U., *J. Org. Chem.*, 1993, vol. 58, p. 6377.
19. Froudakis, G.E. and Stratakis, M., *Eur. J. Org. Chem.*, 2003, p. 359.