RSC Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Adv.*, 2021, **11**, 30841

Halogen-containing heteroaromatic carbenes of the 1,2,4-triazole series and their transformations†

Nataliya V. Glinyanaya,[a] Gennady F. Rayenko,[a] Nikolai I. Korotkikh,*[b] Eduard B. Rusanov,[b] Alexey B. Ryabitsky[c] and Oles P. Shvaika[a]

Received 4th June 2021
Accepted 27th July 2021

DOI: 10.1039/d1ra04337d

rsc.li/rsc-advances

A series of new stable halogenated carbenes, 1-*tert*-butyl-3,4-diaryl-1,2,4-triazol-5-ylidenes, has been synthesized. According to quantum chemical calculations, 4-(2,3,4-trifluorophenyl)-substituted 1-*tert*-butyl-3,4-diaryl-1,2,4-triazol-5-ylidene is the least basic in comparison with the known sterically open stable heteroaromatic carbenes. Upon heating in organic solvents these carbenes undergo a tandem induced reaction thereby forming 5-amidino-1,2,4-triazoles. The interaction of carbenes with benzylidenemalononitrile, propanesultone and phenyl isothiocyanate results in zwitterionic compounds of the 1,2,4-triazole series. The data for X-ray diffraction study of 1-*tert*-butyl-3-phenyl-4-(2,4-difluorophenyl)-1,2,4-triazol-5-ylidene, its protonated salt, complex with copper(I) iodide, related complex of 1-*tert*-butyl-3-phenyl-4-(2-trifluoromethylphenyl)-1,2,4-triazol-5-ylidene, and adduct of 1-*tert*-butyl-3-phenyl-4-(4-bromophenyl)-1,2,4-triazol-5-ylidene and propansultone are given.

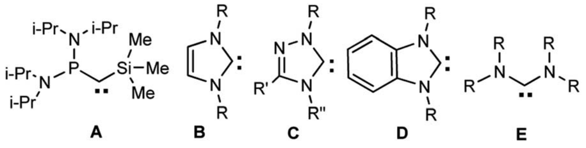
Introduction

The properties of heteroaromatic singlet carbenes have been studied for a long time using *in situ* procedures (without isolation of individual compounds).[1] The discovery of the first stable carbenes by Bertrand (**A**) and Arduengo *et al.* (**B**, R = 1-Ad, Alk, Ar) (Scheme 1) at the turn of the '90s [2,3] gave a powerful impetus to the development of chemistry of these unique divalent carbon compounds. New classes of these compounds have been synthesized, for example, the first 1,2,4-triazolylidene[4] **C** (R, R′, R″ = Ph) and benzimidazol-2-ylidenes **D** (R = 1-Ad, neopentyl)[5–7], acyclic diaminocarbenes **E** (R = *i*-Pr)[8] and later many others (for reviews, see, *e.g.*[9,10]). In addition to the interesting fundamental results a lot of data of applied importance were found: in catalysis, medicine, fluorescent polymer chemistry, *etc.* (see, *e.g.*[11–19]).

Halogen- and especially fluorine-containing heterocyclic singlet carbenes are promising reagents for the synthesis of new drugs. Known haloaromatic compounds have long been included to the arsenal of the most important biologically active compounds, *i.e.* drugs for medicine and preparations for agriculture (pesticides, growth regulators, *etc*). The fluoroaromatic compounds, which compared to other halogenated analogues are not prone to significant metabolism, often exhibit increased biological activities (for reviews, see, *e.g.* [20–23]).

However, the carbene derivatives with fluorine atoms have not been studied sufficiently. The fluorinated compounds of the phosphanyl aryl carbene series **F** were generated by Bertrand *et al.*[24] However, they appeared to be mostly labile and converted into dimers and elimination products even at −70 °C. The most stable derivatives of acyclic carbenes phosphanyl-*o*,*o*-di(trifluoromethyl)phenylcarbene decomposes at 80 °C for several hours and, besides, little accessible. Derivatives of imidazol-2-ylidenes of type **B** with fluorine-containing alkyl groups [R = $CH_2C_6F_5$, $CH_2CH_2C_6F_5$, $CF_3(CF_2)_m(CH_2)_n$, $CF_3O(CF_2CF_2O)_nCF_2CH_2$, $m = 5, 7$; $n = 1, 2$; $CH_2CH_2C_{10}F_{21}$, $CH(Me)C_6F_{13}$], in which the influence of fluorine on the carbene moiety atoms cannot be significant, were described in a series of papers.[25–30] Fluorine-containing imidazolylidenes can be generated from the precursors **G**, **H** of two types obtained on the basis of 2,4-xylidine and hexafluoroacetone (Scheme 2).[31] The formation of a fused carbenoid imidazolinium salt **H** occurred as a side process.

The development of new halogen-containing heterocyclic carbene reagents could expand the possibilities of creating new biologically active compounds.



Scheme 1 First isolated carbenes.

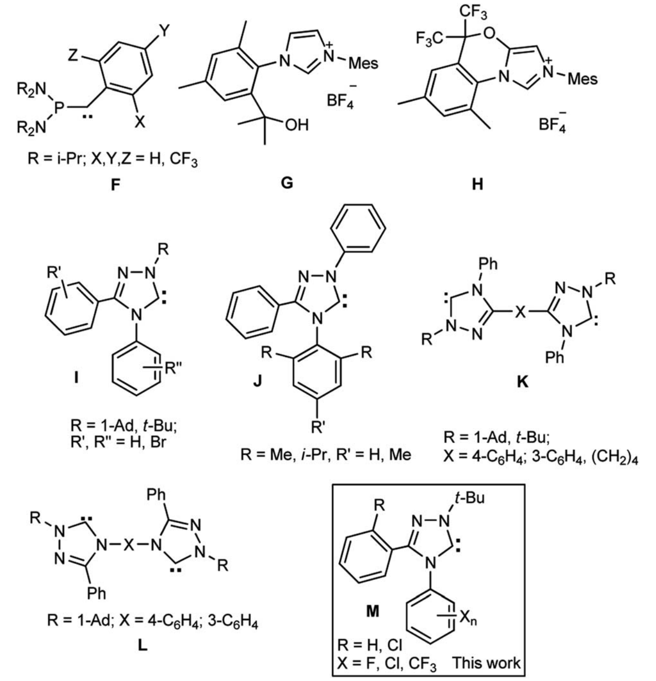
---

[a] The L. M. Litvinenko Institute of Physical Organic and Coal Chemistry, Ukrainian Academy of Sciences, Kyiv, 02160, Ukraine

[b] Institute of Organic Chemistry, Ukrainian Academy of Sciences, Kyiv, 02660, Ukraine. E-mail: nkorotkikh@ua.fm

[c] Life Chemicals Inc., Kyiv, 02660, Ukraine

† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectroscopic data for new compounds and computational details. CCDC 2069434 (**3e**), (2069435 **4e**), 2069436 (**7a**), 2069437 (**9a**) and 2069438 (**9b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra04337d



Scheme 2 Some known fluoro-containing carbenes (F) and precursors (G, H), free triazolylidenes synthesized by the authors (I–L) and a general structure of carbenes synthesized in this work (M).

We set a goal to obtain halogenaromatic, including fluoroaromatic, derivatives of 1,2,4-triazol-5-ylidenes.

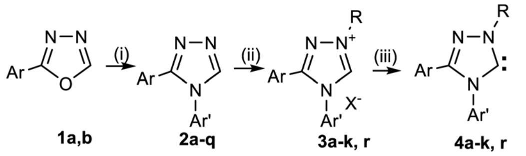
The first individual aromatic carbene of the 1,2,4-triazole series (1,3,4-triphenyl substituted **C**) was synthesized by Enders *et al.*[4] A series of stable derivatives of 1,2,4-triazol-5-ylidenes was extended to their 1-alkyl-3,4-diaryl- (**I**) and 1,3,4-triaryl substituted compounds (**J**), bis-1,2,4-triazol-5-ylidenes (**K**, **L**).[6,32–37] Two first representatives of stable fluorinated 1,2,4-triazolylidenes of type **I** with one fluorine atom in the molecule were characterized in the work.[38]

In this paper we describe:

(1) Synthesis of stable halogen-containing, preferably fluoroaromatic substituted carbenes of a series of 1-*tert*-butyl-3,4-diaryl-1,2,4-triazol-5-ylidenes, including the least basic heteroaromatic singlet stable carbene 1-*tert*-butyl-3-phenyl-4-(2,3,4-trifluorophenyl)-1,2,4-triazol-5-ylidene; (2) synthesis of new derivatives of halogenated carbenes of a series of 1,2,4-triazole (including zwitterionic) *via* the reaction of carbenes with electrophiles; (3) the results of X-ray diffraction study of 1-*tert*-butyl-3-phenyl-4-(2,4-difluorophenyl)-ylidene, its protonated salt, complex with copper(I) iodide, related complex of 1-*tert*-butyl-3-phenyl-4-(2-trifluoromethylphenyl)-1,2,4-triazol-5-ylidene, adduct of 1-*tert*-butyl-3-phenyl-4-(4-bromophenyl)-1,2,4-triazol-5-ylidene and propanesultone.

Synthesis of haloaryl-containing 1,2,4-triazol-5-ylidenes

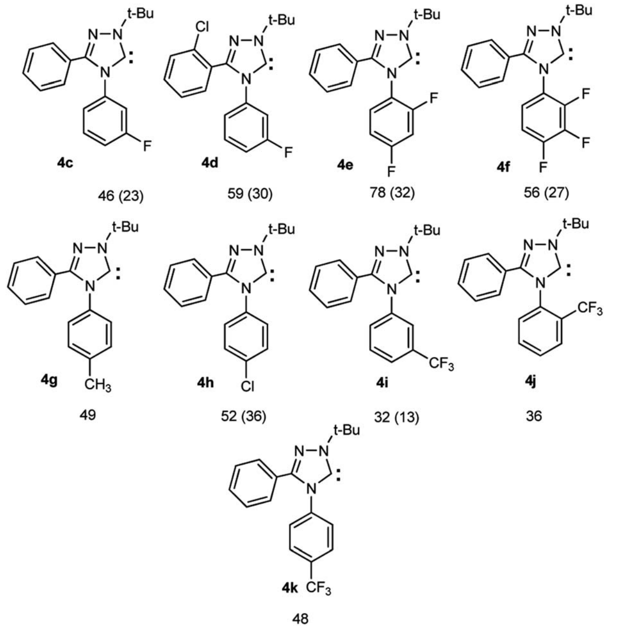
For the synthesis of haloaromatic derivatives of 1,2,4-triazol-5-ylidenes and their non-halogenated analogues, we used the method previously described by us,[6,32–38] including: (1) the preparation of 3,4-diaryl-1,2,4-triazoles **2c–k** by recyclization of 2-aryl-1,3,4-oxadiazoles **1a,b** with arylamines in *o*-dichlorobenzene in the presence of trifluoroacetic acid;[39,40] (2) subsequent quaternization of triazoles **2c–k** with *tert*-butyl iodide in acetic acid, and (3) deprotonation of the resulting salts **3c–k** with potassium *tert*-butoxide in a mixture of toluene and isopropanol thus forming carbenes **4c–k** (Scheme 3). Compounds **2a,b**, **3a,b** and **4a,b**, described earlier,[33,38] are used in this work for discussion, calculations and transformations.



Reagents: (i) Ar′NH$_2$, CF$_3$COOH, *o*-DCB; (ii) (1) *t*-BuI or 1-AdBr, CH$_3$COOH; (2) NaClO$_4$; (iii) *t*-BuOK; *i*-PrOH, PhMe.

1 Ar = Ph (**a**); Ar = 2-ClC$_6$H$_4$ (**b**); **2–4** Ar = Ph, Ar′ = 4-Br–C$_6$H$_4$ (**a**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 4-F–C$_6$H$_4$ (**b**); Ar = Ph, Ar′ = 3-F–C$_6$H$_4$ (**c**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 3-F–C$_6$H$_4$ (**d**); Ar = Ph, Ar′ = 2,4-F$_2$–C$_6$H$_3$ (**e**); Ar = Ph, Ar′ = 2,3,4-F$_3$–C$_6$H$_2$ (**f**); Ar = Ph, Ar′ = 4-CH$_3$–C$_6$H$_4$ (**g**); Ar = Ph, Ar′ = 4-Cl–C$_6$H$_4$ (**h**); Ar = Ph, Ar′ = 3-CF$_3$–C$_6$H$_4$ (**i**); Ar = Ph, Ar′ = 2-CF$_3$–C$_6$H$_4$ (**j**); Ar = Ph, Ar′ = 4-CF$_3$–C$_6$H$_4$ (**k**); **2** Ar = 2-Cl–C$_6$H$_4$, Ar′ = 2,3,4-F$_3$–C$_6$H$_2$ (**l**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 4-Cl–C$_6$H$_4$ (**m**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 3,5-Cl$_2$–C$_6$H$_3$ (**n**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 3,4-Cl$_2$–C$_6$H$_3$ (**o**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 2,3-Cl$_2$–C$_6$H$_3$ (**p**); Ar = 2-Cl–C$_6$H$_4$, Ar′ = 2,6-Cl$_2$–C$_6$H$_3$ (**q**); **3,4a–k** R = *t*-Bu; **3,4r** R = 1-Ad; **2–4r**: Ar = 2,6-*i*-Pr$_2$-C$_6$H$_3$; **3a–k,r** X = ClO$_4$.

The reaction of oxadiazoles **1** with pentafluoroaniline failed because of insufficient reactivity of the latter.



Scheme 3 Synthesis of halogen-containing and related 1-alkyl-3,4-diaryl-1,2,4-triazol-5-ylidenes **4c–k**, their structures and yields of carbenes from 1,2,4-triazoles **2** and from oxadiazoles **1** (in brackets).

The structure of the obtained compounds was confirmed by ^1H and ^{13}C NMR methods, purity – by mass spectrometry and thin layer chromatography, composition – by elemental analysis (see Experimental section in ESI†).

The ^1H NMR spectra of triazoles **2a–q** (in DMSO-d_6) show the characteristic downfield signals of aromatic protons CHN of the triazole ring (δ 8.5–9.1 ppm). The similar ^1H NMR signals of salts **3a–k** in DMSO-d_6 are shifted downfield (δ 10.61–10.81 ppm) due to the electron withdrawing influence of azolium nuclei.

In the mass spectra of compounds **3d–f**, peaks of the respective $[M]^+$ ions are observed, due to the dissociation of the salt into the corresponding 1,2,4-triazolium cation and perchlorate anion. The spectrum of salt **3g** shows three peaks that can be identified as triazolium cation, mono- and diprotonated forms of triazole **2g**. Note for comparison that mass spectra of the corresponding salts by electrospray ionization refer to the corresponding 1,2,4-triazoles.[41]

The ^{13}C NMR spectra of carbenes **4c–k** in C_6D_6 are characterized by signals from the carbene carbon atom at 202.6–211.8 ppm. For carbenes **4c–f, i–k** containing fluorine atoms in the phenyl ring the ^{13}C NMR spectra show the splitting signals of carbon atoms by fluorine atoms. For example, in the spectrum of difluoro-substituted carbene **4e**, the phenyl ring gives the following group of signals: each of the carbon atoms linked to fluorine atoms (2 and 4, respectively) is observed in two groups of signals, respectively, δ 157.0 ppm. (J 12.5 Hz) and 158.5 ppm. (J 12.5 Hz) (for the carbon atom in position 2) and δ 161.1 ppm. (J 10.6 Hz) and 163.5 ppm. (J 10.6 Hz) (for the carbon atom in position 4). Resonance at 104.8 ppm and the spin–spin coupling constants $J_1{}^2$ 23.4 Hz and $J_2{}^2$ 18.7 Hz corresponds to the carbon atom in position 3 of the nucleus; signal at δ 111.5 ppm with constants J^2 22.5 Hz and J^3 3.9 Hz for carbon atoms 5 and 6; resonance with δ 130.4 ppm and the J constant of 8.3 Hz refers to the *ipso* signal of C4N (the carbon atom directly bonded to the nitrogen atom of the triazole rings). Spectra for related fluorine-containing carbenes **4c–f,i–k** are shown in ESI.†

The transformation of salts **3i–k** into carbenes **4i–k** proceeds also smoothly but the contents of free carbenes are somewhat less than those for compounds **4c–h**. Nevertheless, resonances of carbene nuclei were found at 202.6–208.8 ppm (see the ESI†).

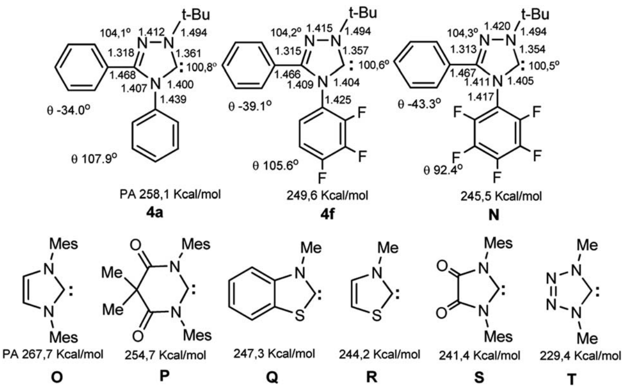
Compounds **4c–h** are stable when stored in a solid state at room temperature for at least 3–4 months in the absence of light, oxygen and moisture to which they are sensitive.

Of particular interest is the effect of fluorine atoms on the properties of carbenes, especially proton affinities associated with their basicities.[42] It is known that halogen atoms, especially fluorine, exhibit a significant electron-donating effect through the π-conjugation chain (for fluorine, σ_R −0.31) and an even stronger electron-withdrawing effect through σ-bonds (σ_I 0.50). The location of fluorine atoms in different positions from the carbene center makes their overall effect on the properties of carbene unobvious.

The calculations of the molecular structures of trifluoro- (**4f**), hypothetical pentafluoro substituted carbenes **N** and the unsubstituted analogue **4a** by DFT method (B3LYP5, 6-311G, RHF in gas phase) showed that the geometric parameters of compounds with substitution of hydrogen atoms with fluorine undergo some changes (Scheme 4).

Thus, for fluorine compounds **4f**, **N** the lengths of the N4–Ar, N1–C5 and N2=C3 bonds are somewhat shortened, while the N4–C5, N4–C3, N1–N2 bonds are lengthened, the angles of rotation of C3 and N4-aromatic nuclei are noticeably increased relative to plane of the triazole ring (the numbering of atoms corresponds to the names of the compounds, see ESI†). Changes in the electronic states of compounds lead to a decrease in the proton affinities of compounds (from PA 258.1 for **4a** to 249.6 kcal mol^{-1} for **4f** and finally to 245.5 kcal mol^{-1} for a related hypothetical pentafluoro-substituted carbene **N**), which indicates a pronounced electron-withdrawing effect of fluorine atoms on the carbene center. For difluoro substituted compound **4e** PA is 253.5 kcal mol^{-1}, for 2-CF_3-substituted **4j** 256.5 kcal mol^{-1}, and for 4-CF_3-compound **4k** 253.9 kcal mol^{-1}. Many of the values for **4e,f,j,N** are substantially less than those for 1,3-dimesitylimidazol-2-ylidene **O** (267.7 kcal mol^{-1}), and even less than for electron depleted 5.5-dimethyl-4,6-dioxopyrimidin-2-ylidene **P** (254.2 kcal mol^{-1}). Probably, the influence of fluorine atoms to the carbene centre is carried out by dominating electron withdrawing −I effect of fluorine atoms (leading to a significant depletion of electron density of the nuclei) compared to the fluorine +M effect *via* the conjugation chain. The enthalpies of dimerization of compounds **4e,f** are significantly positive (8.8 and 11.0 kcal mol^{-1}, respectively at the level of B3LYP5, 6-31G, RHF), which indicates the impossibility of their dimerization. Nevertheless, they are closer to the instability limit compared to the unsubstituted analogue **4a** (12.4 kcal mol^{-1}).[43]

According to quantum chemical calculations, an increase in the electron donation effect in nucleophilic carbenes leads to an increase in their dimerization energies (electronic and steric parameters, ESP).[43–46] Therefore, the demonstration of the stability of carbenes with low PA is unusual. The properties of carbenes **4e,f,j** feature that having close values of PA compared to the sterically open carbenes (*e.g.*, of benzothiazole and thiazole series **Q**, **R**), they are stable and, unlike the latters, do not



Scheme 4 Bond lengths (Å), some internal and dihedral angles (θ) and proton affinities for carbenes **4f**, **N** compared with those for carbene **4a** and a series of carbene analogues (**O–T**) according to calculations by the DFT, B3LYP5, 6-311G, RHF method.

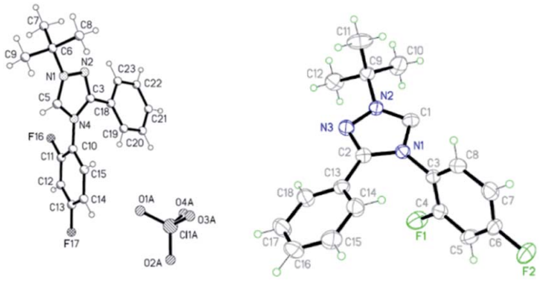


Fig. 1 X-ray structures of salt **3e** and carbene **4e**.

dimerize. Note, that the sterically shielded 3-(2,6-diisopropyl)-4,5-dimethylthiazol-2-ylidene isolated by Arduengo *et al.*[47] has PA 256.8 kcal mol^{-1}. The sterically shielded nonaromatic carbene **S**, generated in the work[48] and the hypothetical tetrazol-5-ylidene **T** exhibit the least proton affinities (PA 241.4 and 229.4 kcal mol^{-1}, respectively) compared with the synthesized heteroaromatic carbenes. However, the first carbene was not isolated due to its dimerization, and the second (like its derivatives) is inaccessible due to the decomposition of the tetrazolylidene ring (into carbodiimide and nitrogen) under the action of nucleophiles.[9–11] A number of fused 1,2,4-triazol-5-ylidenes with the lowest PA values (up to 241.8 kcal mol^{-1}) have been studied by determining the gas phase acidity of the corresponding salt precursors.[49] However, these compounds have not yet been isolated.

Thus, the synthesis of di- and trifluorinated 1,2,4-triazol-5-ylidenes **4e,f** is a novel step in the study of low basic carbenes.

The X-ray diffraction study results for carbene **4e** and their precursor **3e** are presented below.

Difluorinated triazolium perchlorate **3e** is a protonated carbene **4e** (Fig. 1). The crystals of the salt were grown from acetonitrile. According to X-ray diffraction data, the structure of the cation is aromatic, planar with close to double C5–N1 and C3–N2 bonds (Table 1). The angle at the carbenoid atom C5 106.9° is far from the carbene one (100–102°). The C3 aromatic nucleus is located at an angle of 23.4° (C3–C18 bond order 1.345), the N4 nucleus – at an angle of 71.6° (N4–C10 bond order 1.224).

The crystals of carbene **4e** were grown from hexane. According to X-ray diffraction study, the structure of carbene **4e** is aromatic, planar with close to the double bond C2–N3 and some longer C1–N2 bonds (Fig. 1 and Table 2).

Table 1 Bond lengths and angles in the X-ray structure of salt **3e**

Bond	Bond length, Å	Bond order[a]	Angle	Angle value, °
C5–N1	1.300(5)	2.000	N1C5N4	106.9(3)
C5–N4	1.351(5)	1.707	N2C3N4	109.4(3)
C3–N2	1.313(5)	1.925	N1N2C3N4	0.1(4)
C3–N4	1.380(5)	1.540	C6N1N2C3	176.3(6)
N1–N2	1.365(4)	1.431	C18C3N2N1	−178.6(3)
C3–C18	1.466(5)	1.345	C19C18C3N2	156.6(4)
N4–C10	1.435(5)	1.224	C11C10N4C5	108.4(4)
C6–N1	1.502(5)	0.839	—	—

[a] Calculated from the linear dependence of bond orders and the X-ray bond lengths of simple model compounds.[33,50]

Table 2 Bond lengths and angles in the X-ray structure of carbene **4e**

Bond	Bond length, Å	Bond order	Angle	Angle value, °
C1–N2	1.346(3)	1.736	N1C1N2	100.14(17)
C1–N1	1.390(3)	1.483	N1C2N3	109.82(17)
C2–N3	1.313(2)	1.925	N1C1N2N3	−0.7(2)
C3–N4	1.383(3)	1.523	N2N3C2N1	1.0(2)
N1–N2	1.393(2)	1.287	N2N3C2C13	−178.05(19)
N2–C9	1.494(3)	0.885	N1C2C13C14	33.6(3)
C2–C13	1.476(3)	1.294	C2N1C3C4	76.9(3)
C3–N1	1.436(3)	1.218	—	—

The C1–N2 bond order (1.746) indicates the presence of about 74% of the ylide form. The angle at the carbene atom is 100.1°. The C2-aromatic nucleus is located at an angle of 33.6° to the plane of the triazole ring (C2–C13 bond order 1.294), the N1 nucleus – at an angle of 76.9° (N1–C3 bond order 1.218).

Thus, we first synthesized a series of stable carbenes including fluorine containing heteroaromatic compounds **4e,f** having the reduced proton affinities.

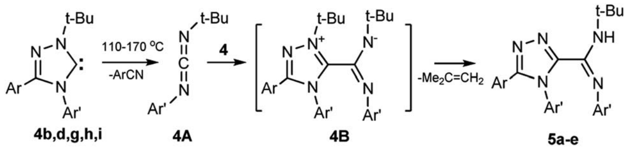
Transformations of haloaryl-containing 1,2,4-triazol-5-ylidenes

Earlier, the authors of this article found that 1-alkyl-3,4-diaryl-substituted 1,2,4-triazol-5-ylidenes undergo tandem (cascade) reaction upon heating to form 5-amidino-1,2,4-triazoles.[33] However, the reaction of carbenes containing fluorine atoms in aromatic nuclei has not yet been studied.

To establish the possibility of the reaction for halogenated carbenes, compounds **4b,d,h,i** or a related tolyl-substituted compound **4g**, were heated with a gradual increase in temperature to 130–170 °C in decane. As a result, tandem induced transformation (Scheme 5) proceeds through intermediate carbodiimides **4A** and zwitterionic compounds **4B** thereby forming 5-amidino-1,2,4-triazoles **5a–e**, including fluorinated compounds **5a,b,d.**

4b, **5a** Ar = C_6H_4Cl-2, Ar′ = C_6H_4F-4; **4d**, **5b** Ar = C_6H_4Cl-2, Ar′ = C_6H_4F-3; **4h**, **5c** Ar = C_6H_5, Ar′ = C_6H_4Cl-4; **4i**, **5d** Ar = C_6H_5, Ar′ = C_6H_4-CF_3-3; **4g**, **5e** Ar = C_6H_5, Ar′ = C_6H_4Me-4.

The easier transformation of the fluorinated carbenes **4b,d,i** compared with the methyl-substituted analogue **4g** should be noted. A rapid increase in temperature and heating at 130–170 °C increases the yield of conversion products of carbene, carbodiimide, and benzonitrile (in this case, carbene has little time to react with carbodiimide).



Scheme 5 Tandem induced reaction of 1-*tert*-butyl-3,4-diaryl-1,2,4-triazol-5-ylidenes **4b,d,g,h,i**.

The composition and structure of 5-amidino-1,2,4-triazoles **5a–e** were confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry (see ESI†). Earlier, the structure of their analogue (R = C_6H_5, R′ = *p*-C_6H_4Br) was established by X-ray diffraction study.[33]

The ^{1}H NMR spectra of compounds **5a–e** show the proton signals of *tert*-butyl groups that are shifted upfield (δ 1.56–1.67 ppm) relative to the salt ones, characteristic signals of NH protons observed in the range of δ 6.6–6.9 ppm (in the spectra of compounds **5a,c,d** they are superimposed on the signals of aromatic protons). The resonances of *tert*-butyl group in the ^{13}C NMR spectra are detected in the range of 28.0–28.5 and 52.7–58.7 ppm. The signals of amidine carbon atoms are observed at 134.4–138.9 ppm.

The mass spectra of amidinotriazoles **5a,e** contain molecular ions characteristic of the given structures.

Thus, the reaction of chloro and fluoro substituted 1-*tert*-butyl-3,4-diaryl-1,2,4-triazol-5-ylidenes **4b,c,d,h,i** proceeds quite efficiently, leading to chlorinated and fluorinated amidinotriazoles **5a–d** (up to 6 fluorine atoms in a **5d** molecule) promising for biological research.

From the standpoint of the synthesis of new types of heterocyclic compounds the study of carbene reactions with compounds containing activated multiple bonds and cyclic ether groups is of particular interest. To assess the synthetic possibilities of halogenated heterocyclic carbenes, their reactions with benzylidenemalononitrile, propanesultone, and phenylisothiocyanate were carried out.

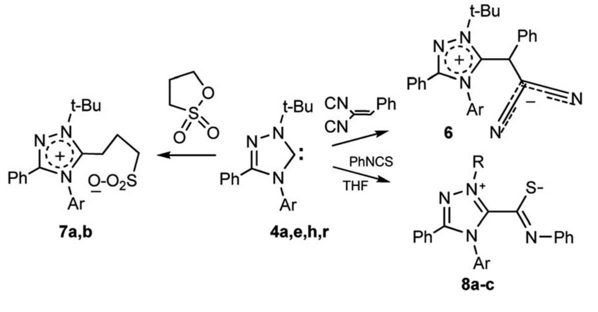
As a result of the transformation of carbene **4a** with benzylidenemalononitrile a zwitterionic compound **6** was isolated (Scheme 6), which undergoes changes upon storage (with darkening of the substance).

4a, **6**, **7a** Ar = 4-Br-C_6H_4; **4h**, **7b** Ar = 4-ClC_6H_4; **4a**, **8a** R = *t*-Bu, Ar = 4-Br-C_6H_4; **4e**, **8b** R = *t*-Bu, Ar = 2,4-F_2-C_6H_3; **4r**, **8c** R, Ar = 1-Ad, 2,6-*i*-Pr_2-C_6H_3

Nevertheless, it was possible to record ^{1}H-NMR spectra of compound **6**, in which specific signals of the protons of *tert*-butyl group (δ 1.72 ppm) and proton CHPh (δ 5.94 ppm) were detected.

The reaction of carbenes **4a,h** with propanesultone proceeds through ring opening, thereby forming zwitterionic compounds **7a,b** (Scheme 6).

The ^{1}H NMR spectrum of compound **7a** revealed characteristic signals of the *tert*-butyl group (δ 1.84 ppm), the methylene group directly bonded to the triazole ring (δ 3.29 ppm), central methylene groups of the propanesulfonate fragment (δ 2.08 ppm) and a group associated with a sulfur atom (δ 2.36 ppm). In the ^{13}C NMR spectrum of compound **7b** (in solid state), the signals are identified as follows: *tert*-butyl group with δ 30.3, 31.3 ppm, for carbon atoms of methyl groups and δ 67.2, 67.6 ppm, for *ipso*-carbon atom, respectively. The resonance of the carbon atom of the propanesulfonate group bound to the triazole ring is observed at δ 25.3–36.9 ppm. The carbon atom associated with sulfur shows signals at δ 50.6, 50.8 ppm, and the central carbon atom gives a signal at δ 23.8, 25.5 ppm. The resonances of the triazole ring are detected at δ 136.2, 137.2 ppm (C3), and 152.3, 153.3 ppm (C5), respectively.



Scheme 6 Reactions of carbenes **4a,h** with benzylidenemalononitrile, propanesultone and phenylisothiocyanate.

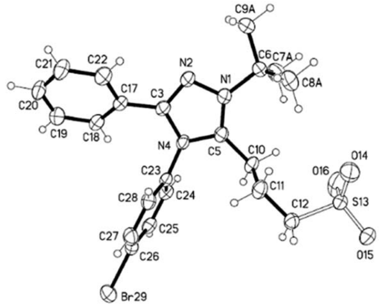


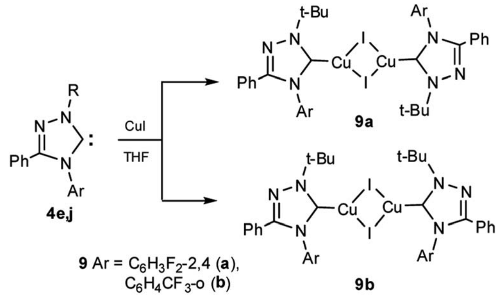
Fig. 2 X-ray structure of zwitterion **7a**.

The crystals of compound **7a** were grown from acetonitrile. The structure of the molecule is shown in Fig. 2 and Table 3. According to these data the triazole ring is planar, aromatic nuclei are turned around at 38.5° (C3–C17 bond order 1.376) and 77° (N4–C23 bond order 1.149), respectively. The ring bonds are strongly conjugated (bond orders 1.983, 1.851, 1.701, 1.552).

The reaction with phenyl isothiocyanate proceeds similarly. Previously the transformation was carried out *in situ* (see, for example[1]). At the level of individual carbenes it was studied by Enders *et al.* for 1,3,4-triphenyl-1,3,4-triazol-5-ylidene.[51] Later Bielawski *et al.* showed that the more sterically protected 1,3-dimesitylimidazol-2-ylidene also readily reacts with phenylisothiocyanate to form a zwitterion.[52]

Table 3 Bond lengths and angles in the X-ray structure of zwitterion **7a**

Bond	Bond length Å	Bond order	Angle	Angle value, °
C5–N1	1.326(4)	1.851	N1C5N4	105.7(3)
C5–N4	1.352(4)	1.701	C1N1C2	109.7(3)
C3–N4	1.378(4)	1.552	C5N1N2C3	0.4(4)
C3–N2	1.303(4)	1.983	N1N2C3N4	−1.4(4)
N1–N2	1.374(4)	1.385	N4C5N1C6	176.4(3)
N4–C23	1.448(4)	1.149	C5N4C23C24	−77.0(4)
N1–C6	1.509(4)	0.851	N2C3C17C22	−38.5(5)
C3–C17	1.460(5)	1.376	—	—
C5–C10	1.493(4)	1.208	—	—
S13–O14	1.460(3)	—	—	—



Scheme 7 Reaction of carbenes **4e,j** with CuI

However, the transformation of sterically strongly shielded and fluorinated systems with reduced basicities has not yet been studied.

For comparison, two directions of the transformation of carbene were observed with related carbodiimides: into zwitterionic compounds (reagent ratio 1 : 1) and spirocyclic systems (1 : 2).[33]

We found that bromo- and difluoro-substituted triazolylidenes **4a,e** and sterically shielded 1-adamantyl-3-phenyl-4-(2,6-diisopropylphenyl)-1,2,4-triazol-5-ylidene **4r** (synthesized in the work[36]) readily reacts with phenyl isothiocyanate to form the corresponding zwitterions **8a–c** (Scheme 6).

The structures of compounds **8a–c** were confirmed by ^{1}H and ^{13}C NMR spectroscopy (see ESI†). The most characteristic signals in the ^{13}C NMR spectrum of the synthesized zwitterions are carbon signals of the N=C–S fragment (165.6–166.5 ppm).

Thus, halogen-containing 1,2,4-triazol-5-ylidenes react with electrophilic benzylidenemalononitrile, phenylisothiocyanate and propanesultone, thereby forming halogenated zwitterionic compounds **6–8**.

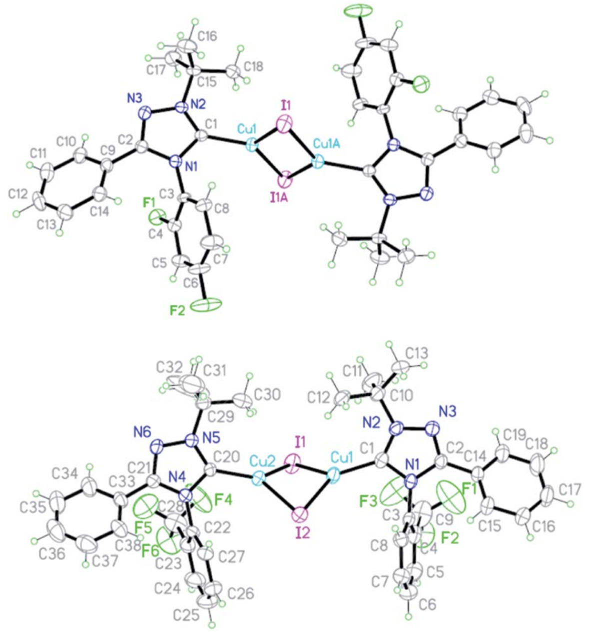


Fig. 3 X-Ray structures of carbene complexes **9a,b**.

Table 4 Bond lengths and angles in the structure of complex **9a**

Bond	Bond length, Å	Bond order	Angle	Value, °
C1–N1	1.381(5)	1.534	N1C1N2	102.7(3)
C1–N2	1.329(5)	1.833	C1N1C2	109.3(3)
C2–N3	1.307(5)	1.960	C1N1C2N3	0.0(5)
C2–N1	1.380(5)	1.540	C1N2N3C2	−1.3(4)
C3–N1	1.432(5)	1.241	C15N2C1N1	176.1(3)
C15–N2	1.500(5)	0.851	N3C2C9C10	34.6(6)
C9–C2	1.473(6)	1.310	C2N1C3C4	61.7(6)
N2–N3	1.391(5)	1.297	—	—
C1–Cu1	1.936(4)	—	—	—
Cu1–I1	2.5553(6)	—	—	—

The formation of complexes with copper(I) iodide **9a,b** is exemplified by the reactions of fluorinated carbenes **4e,j** (Scheme 7). These complexes are also obtained under the interaction of salts **3e,j** with copper(I) iodide in the presence of potassium carbonate in acetonitrile.

The ^{13}C NMR spectra revealed signals of carbenoid carbon atoms in the range of 184–185 ppm.

The crystals of complexes **9a,b** were grown from acetonitrile.

According to X-ray diffraction data, the molecule of complex **9a** has a dimeric state with an interaction between the metal iodide fragments of two monomeric fragments and a *trans*-configuration. The structure of the azole rings in the complex is planar (Fig. 3), the order of the C5–N1 bond (1.833) indicates a high content of the ylide form of the carbene in the complex (83%) (Table 4).

The angle at the carbene atom (102.7°) is close to that for free carbene **4e** (100.1°). The C2-aromatic nucleus is located at an angle of 34.6° (C2–C9 bond order 1.310), the N1 bond – at an angle of 61.7° (N1–C3 bond order 1.241). The C1–Cu1 bond length (1.936 Å) is closer to the sum of the radii of covalent atoms (2.05 Å) than to the sum of the covalent radius of a carbon atom and the ionic radius of copper (1.47 Å). The Cu1–I1 bond length (2.555 Å) is closer to the sum of the ionic radii of copper and iodine (2.66 Å) than to the sum of the covalent radii (2.75 Å).

The molecule of complex **9b** has also a dimer state but, on the contrary to **9a**, a *cis*-configuration (Fig. 3). In addition to the configuration, the difference between structures **9a,b** lies in the

Table 5 Bond lengths and angles in the structure of complex **9b**

Bond	Bond length, Å	Bond order	Angle	Value, °
C1–N1	1.367(8)	1.615	N1C1N2	101.5(6)
C1–N2	1.339(8)	1.776	C1N1C2	109.8(6)
C2–N3	1.292(8)	2.046	C1N1C2N3	1.4(8)
C2–N1	1.383(8)	1.523	C1N2N3C2	−0.8(8)
N2–N3	1.360(7)	1.456	N1C1N2C10	174.9(6)
C3–N1	1.451(8)	1.132	N3C2C14C15	144.3(8)
C10–N2	1.503(9)	0.833	C2N1C3C4	83.2(8)
C14–C2	1.471(9)	1.320	—	—
C1–Cu1	1.933(7)	—	—	—
Cu1–I1	2.5580(10)	—	—	—

lower order of the C1–N2 bond (1.776) in **9b**, which indicates a lower content of the ylidic form (78%) (Table 5).

The angle at the carbene atom (101.5°) is close to that for free carbene. The C2 aromatic nucleus is located at an angle of 35.7° (C2–C14 bond order 1.320), the N1 nucleus – at an angle of 83.2° (N1–C3 bond order 1.132). The bond length C1–Cu1 (1.933 Å) and Cu1–I1 (2.558 Å) are close to those for complex **9a**.

Conclusion

As a result of this study, nine new individual halogen-containing derivatives of 1,2,4-triazol-5-ylidene, including fluorine-containing compounds, were synthesized. The most fluorinated in the aromatic ring carbene 1-*tert*-butyl-3-phenyl-4-(2,3,4-trifluorophenyl)-1,2,4-triazol-5-ylidene **4f** is the least basic according to theoretical data (PA 249.6 kcal mol^{-1}) in comparison with known derivatives of stable isolable carbenes. Thus, the lower limit of the basic properties of stable individual carbenes has been extended. Some of the properties of these compounds have been studied. The halogenated derivatives of 1,2,4-triazol-5-ylidenes undergo a tandem induced reaction into 5-amidino-1,2,4-triazoles, and afford halogenated heterocyclic zwitterionic compounds with electrophiles (benzylidenemalononitrile, propanesultone and phenyl isothiocyanate). The carbene complexes with copper(I) iodide have been prepared starting from the individual carbenes or *in situ* reactions. These reactions have opened up new possibilities for the synthesis of halogenated heterocyclic compounds for biological tests and other purposes.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the Ukrainian National Academy of Sciences for financial support (The Program of Fundamental Research "New Functional Substances and Materials for Chemical Engineering", grant No. 22-21).

References

1 O. P. Shvaika, N. I. Korotkikh and A. F. Aslanov, *Chem. Heterocycl. Compd.*, 1992, **9**, 1155–1170.

2 (*a*) A. Igau, H. Grutzmacher, A. Baceiredo and G. Bertrand, *J. Am. Chem. Soc.*, 1988, **110**, 6463–6466; (*b*) A. Igau, A. Baceiredo, G. Trinquier and G. Bertrand, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 621–622; (*c*) G. R. Gillette, A. Baceiredo and G. Bertrand, *Angew. Chem., Int. Ed.*, 1990, **102**, 1429–1431.

3 (*a*) A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**(1), 361–363; (*b*) A. J. Arduengo, H. V. R. Dias, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1992, **114**(14), 5530–5536.

4 D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J. P. Melder, K. Ebel and S. Brode, *Angew. Chem., Int. Ed.*, 1995, **34**, 1021–1023.

5 F. E. Hahn, L. Wittenbecher, R. Boese and D. Blaser, *Chem.– Eur. J.*, 1999, **82**, 1931–1935.

6 (*a*) N. I. Korotkikh, G. F. Rayenko and O. P. Shvaika, *Proceed. 17-th Intern. Congress of Heterocyclic Chemistry*, 1999, Vienna; (*b*) N. I. Korotkikh, G. F. Rayenko and O. P. Shvaika, *Rep. Ukr. Acad. Sci.*, 2000, **2**, 135–140.

7 N. I. Korotkikh, G. F. Raenko, T. M. Pekhtereva, O. P. Shvaika, A. H. Cowley and J. N. Jones, *Rus. J. Org. Chem.*, 2006, **42**(12), 1822–1833.

8 R. W. Alder, P. P. Allen, M. Murray and A. G. Orpen, *Angew. Chem., Int. Ed.*, 1996, **35**, 1121–1123.

9 (*a*) D. Bourissou, O. Guerret, F. P. Gabbai and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39–92; (*b*) J. Vignolle, X. Cattoen and D. Bourissou, *Chem. Rev.*, 2009, **109**, 3333–3384; (*c*) M. Melaimi, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.*, 2010, **49**, 8810–8849; (*d*) D. Martin, M. Melaimi, M. Soleilhavoup and G. Bertrand, *Organometallics*, 2011, **30**, 5304–5313; (*e*) M. C. Jahnke and F. E. Hahn, N-Heterocyclic carbenes: from laboratory curiosities to efficient synthetic tools, *RSC Catal. Ser.*, 2011, 1–41; (*f*) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485–496.

10 N. I. Korotkikh, A. H. Cowley, J. A. C. Clyburne, K. N. Robertson, V. S. Saberov, N. V. Glinyanaya, G. F. Rayenko and O. P. Shvaika, *ARKIVOC*, 2017, 257–355.

11 (*a*) N. I. Korotkikh and O. P. Shvaika, *Carbene and Carbene Complex Catalysis of Organic Reactions*, DonNU, Donetsk, Ukraine, 2013, p. 372; (*b*) N. I. Korotkikh and O. P. Shvaika, *Organic Reactions Catalysis by Carbenes and Metal Carbene Complexes*, LAP Lambert Academic Publishing, 2015, p. 385.

12 D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655.

13 *N-Heterocyclic Carbenes in Synthesis*, ed. S. P. Nolan, Wiley VCH Verlag GmbH & Co KgaA, Weinheim, 2006, 68.

14 J. Izquierdo, G. E. Hutson, D. T. Cohen and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2012, **51**, 11686–11698.

15 M. J. Fuchter, *Chem.– Eur. J.*, 2010, **16**, 12286–12294.

16 P.-C. Chiang, and J. Y. W. Bode, in *RSC Catalysis Series No. 6: N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, ed. S. Diez-Gonzalez, Royal Society of Chemistry, 2013, ch. 14, p. 399.

17 A. R. Kapdi and I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2014, **43**, 4751–4777.

18 R. Visbal and M. C. Gimeno, *Chem. Soc. Rev.*, 2014, **43**, 3551–3574.

19 S. N. Riduan and Y. Zhang, *Chem. Soc. Rev.*, 2013, **42**, 9055–9070.

20 M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**(19), 10633–10640.

21 H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi and V. A. Soloshonok, *Chem.–Eur. J.*, 2019, **25**, 11797–11819.

22 H. Mei, A. M. Remete, Y. Zou, H. Moriwaki, S. Fustero, L. Kiss, V. A. Soloshonok and J. Han, *Chin. Chem. Lett.*, 2020, **31**, 2401–2413.

23 W. R. Dolbier, *J. Fluorine Chem.*, 2005, **126**, 157–163.

24 E. Despagnet-Ayoub, S. Sole, H. Gornitzka, A. B. Rozhenko, W. W. Schoeller, D. Bourissou and G. Bertrand, *J. Am. Chem. Soc.*, 2003, **125**, 124–130.

25 L. Xu, W. Chen, J. F. Bickley, A. Steiner and J. Xiao, *J. Organomet. Chem.*, 2000, **598**, 409–416.

26 T. Fukuyama, M. Arai, H. Matsubara and I. Ryu, *J. Org. Chem.*, 2004, **69**, 8105–8107.

27 M. Skalický, M. Rybáčková, O. Kysilka, M. Kvíčalová, J. Cvačka, J. Čejka and J. Kvíčala, *J. Fluorine Chem.*, 2009, **130**, 966–973.

28 A. Fürstner, L. Ackermann, B. Gabor, R. Goddard, C. W. Lehmann, R. Mynott, F. Stelzer and O. R. Thiel, *Chem.–Eur. J.*, 2001, **7**, 3236–3253.

29 M. Skalický, V. Skalická, M. Rybáčková, M. Kvíčalová, J. Cvačka, A. Březinová and J. Kvíčala, *Organometallics*, 2012, **31**, 1524–1532.

30 V. Kolaříková, O. Šimůnek, M. Rybáčková, J. Cvačka, A. Březinová and J. Kvíčala, *Dalton Trans.*, 2015, **44**, 19663–19673.

31 M. A. Topchiy, M. A. Zotova, S. M. Masoud, A. K. Mailyan, I. V. Ananyev, S. E. Nefedov, A. F. Asachenko and S. N. Osipov, *Chem.–Eur. J.*, 2017, **23**, 6663–6674.

32 N. I. Korotkikh, G. F. Rayenko, O. P. Shvaika, T. M. Pekhtereva, A. H. Cowley, J. N. Jones and C. L. B. Macdonald, *J. Org. Chem.*, 2003, **68**(14), 5762–5765.

33 N. I. Korotkikh, N. V. Glinyanaya, A. H. Cowley, J. A. Moore, A. V. Knishevitsky, T. M. Pekhtereva and O. P. Shvaika, *ARKIVOC*, 2007, **16**, 156–172.

34 (*a*) N. I. Korotkikh, A. V. Kiselyov, G. F. Rayenko, M. M. Oliynik and O. P. Shvaika, *Rep. Ukr. Acad. Sci.*, 2003, **6**, 142–146; (*b*) A. V. Kiselyov, N. I. Korotkikh, A. H. Cowley, J. A. Moore, T. M. Pekhtereva and O. P. Shvaika, *ARKIVOC*, 2008, **15**, 329–334.

35 A. V. Knishevitsky, N. I. Korotkikh, A. H. Cowley, J. A. Moore, T. M. Pekhtereva, O. P. Shvaika and G. Reeske, *J. Organomet. Chem.*, 2008, **693**, 1405–1411.

36 N. V. Glinyanaya, V. S. Saberov, N. I. Korotkikh, A. H. Cowley, R. R. Butorac, D. A. Evans, T. M. Pekhtereva, A. F. Popov and O. P. Shvaika, *Dalton Trans.*, 2014, **43**, 16227–16237.

37 N. V. Glinyanaya, N. I. Korotkikh, A. H. Cowley, O. Williams, R. A. Jones, V. M. Lynch, A. V. Kiselyov, G. F. Rayenko, M. A. Derevenets, A. B. Ryabitsky, O. Esarte Palomero and O. P. Shvaika, *ChemistrySelect*, 2018, **3**, 5244–5248.

38 N. I. Korotkikh, A. H. Cowley, J. A. Moore, N. V. Glinyanaya, I. S. Panov, G. F. Rayenko, T. M. Pekhtereva and O. P. Shvaika, *Org. Biomol. Chem.*, 2008, **6**, 195–199.

39 N. I. Korotkikh, A. V. Kiselyov, A. V. Knishevitsky, G. F. Rayenko, T. M. Pekhtereva and O. P. Shvaika, *Chem. Heterocycl. Compd.*, 2005, **7**, 1026–1032.

40 N. I. Korotkikh, O. P. Shvaika, G. F. Rayenko, A. V. Kiselyov, A. V. Knishevitsky, A. H. Cowley, J. N. Jones and C. L. B. Macdonald, *ARKIVOC*, 2005, **8**, 10–43.

41 N. Lyapchenko, R. Franski, G. Schroeder, T. Kozik, O. P. Schvaika, A. V. Kiselyov and N. I. Korotkikh, *Int. J. Mass Spectrom.*, 2003, **228**, 61–68.

42 A. M. Magill, K. J. Cavell and B. F. Yates, *J. Am. Chem. Soc.*, 2004, **126**, 8717–8724.

43 N. Korotkikh, G. Rayenko, V. Saberov, V. Yenya, N. Glinyanaya, M. Nechitailov and O. Shvaika, *Proceed. T.G. Shevchenko Sci. Commun., Ser. Chem.*, 2019, **56**, 23–34, DOI: 10.37827/ntsh.chem.2019.56.023.

44 N. Korotkikh, G. Rayenko, V. Saberov and O. Shvaika, *Proceed. T.G. Shevchenko Sci. Commun., Ser. Chem.*, 2019, **56**, 7–22, DOI: 10.37827/ntsh.chem.2019.56.007.

45 N. Korotkikh, G. Rayenko, V. Saberov, V. Yenya, A. Knishevitsky and O. Shvaika, *Proceed. T.G. Shevchenko Sci. Commun., Ser. Chem.*, 2019, **56**, 35–44, DOI: 10.37827/ntsh.chem.2019.56.035.

46 N. I. Korotkikh, G. F. Rayenko, V. Sh. Saberov, V. I. Yenya and O. P. Shvaika, *J. Org. Pharm. Chem.*, 2019, **17**(4), 28–36, DOI: 10.24959/ophcj.19.183372.

47 A. J. Arduengo, J. R. Goerlich and W. J. Marshall, *Liebigs Ann./Recl.*, 1997, 365–374.

48 M. Braun, W. Frank, G. J. Reiss and C. Ganter, *Organometallics*, 2010, **29**, 4418–4420.

49 Y. Niu, N. Wang, A. Muñoz, J. Xu, H. Zeng, T. Rovis and J. K. Lee, *J. Am. Chem. Soc.*, 2017, **139**, 14917–14930.

50 M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw Book Co., N.-Y., 1969, p. 216.

51 D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Liebigs Ann. Chem.*, 1996, 2019–2028.

52 B. C. Norris, D. G. Sheppard, G. Henkelman and C. W. Bielawski, *J. Org. Chem.*, 2011, **76**, 301–304.