Peculiarities of the cascade cleavage of the polarized C≡C-fragment in *α*-ketoacetylenes on reaction with ethylene diamine

Sergei F. Vasilevsky,[a,b]* Maria P. Davydova,[a] Denis N. Tomilin,[c] Lyubov N. Sobenina,[c] Victor I. Mamatuyk,[b,d] and Nadezhda V. Pleshkova[d]

[a] *V.V. Voevodsky Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 3 Institutskaya str., 630 090 Novosibirsk, Russian Federation*

[b] *Novosibirsk State University, 2 Pirogova Str., 630 090, Novosibirsk, Russian Federation*

[c] *A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky str., 664 033 Irkutsk, Russian Federation*

[d] *N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Acad. Lavrent'eva, 630 090 Novosibirsk, Russian Federation*

E-mail: vasilev@kinetics.nsc.ru

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.663

Abstract

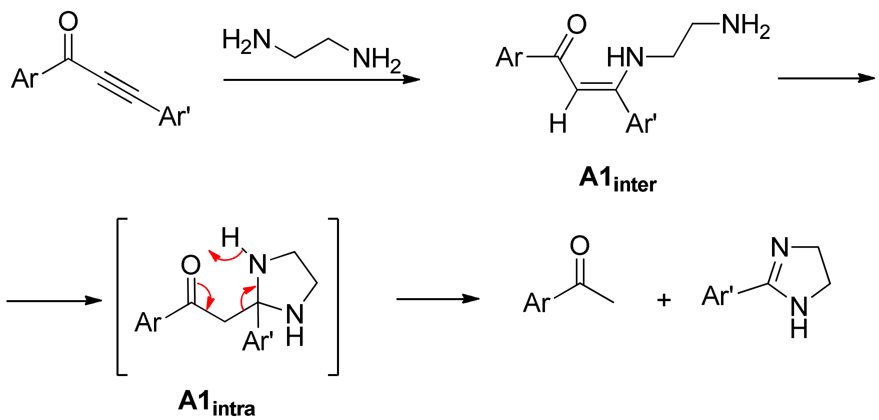
The reaction of diarylketoacetylenes with ethylenediamine (EDA) leads to arylmethylketones and 2-substituted imidazoline derivatives. This transformation involves complete cleavage of the triple bond via initial intermolecular Michael-addition with subsequent intramolecular Michael-addition. Final fragmentation can be presented as a retro-Mannich reaction, accompanied by three formal reductive stages (formation of three C-H bonds), while the other carbon undergoes a formal oxidation, in which three C-N bonds (C-N and C=N) are formed.

Keywords: *α*-Ketoacetylenes, ethylenediamine, Michael addition, triple bond cleavage, arylmethylketones, 4,5-dihydro-1*H*-imidazoles

Introduction

The high and unique reactivity of compounds with a triple bond motivates their extensive application in organic synthesis, medicinal chemistry, biotechnology and material science.[1] *α*-Ketoacetylenes possess additional synthetic potential:[2,3] Owing to the increased electrophilicity of the acetylenic fragment and its proximity to the carbonyl group, these compounds represent excellent models for studying the factors controlling regioselectivity of their addition reactions. In the reactions with nucleophilic reagents, such structures are prone to facile heterocyclization.[4] From the fundamental point of view, this contributes to a deeper understanding of their reactivity and allows the data relating to Baldwin's rules (explaining the directions of cyclization under alternative routes of reactions) to be extended. This area of organic chemistry has attracted considerable research attention.[5]

Earlier we reported[6,7] that the reaction of diarylketoacetylenes with EDA affords acetophenones and 2-substituted imidazoline derivatives. This fragmentation involves total cleavage of the triple bond via three formal reductive stages to form three C-H bonds, whereas other carbon undergoes formal oxidation, *i.e.* three C-N bonds (C-N and C=N) are formed (Scheme 1).



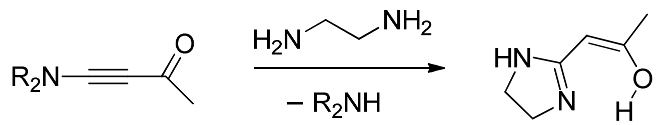
Scheme 1. Proposed pathway for the complete disproportionation of alkyne moiety.

Results and Discussion

In previous work we studied *α*-ketoacetylenes bearing aryl substituents in the ketone and alkyne counterparts of the molecule, in all cases the above cleavage of the substrate to a 2-substituted imidazoline being observed.

To confirm the generality of this reaction as well as to elucidate the effects of electronic and steric factors, we chose substrates containing 5-membered heterocyclic donor substituents (pyrazole, pyrrole) and 6-membered acceptor *p*-bromophenyl fragment.

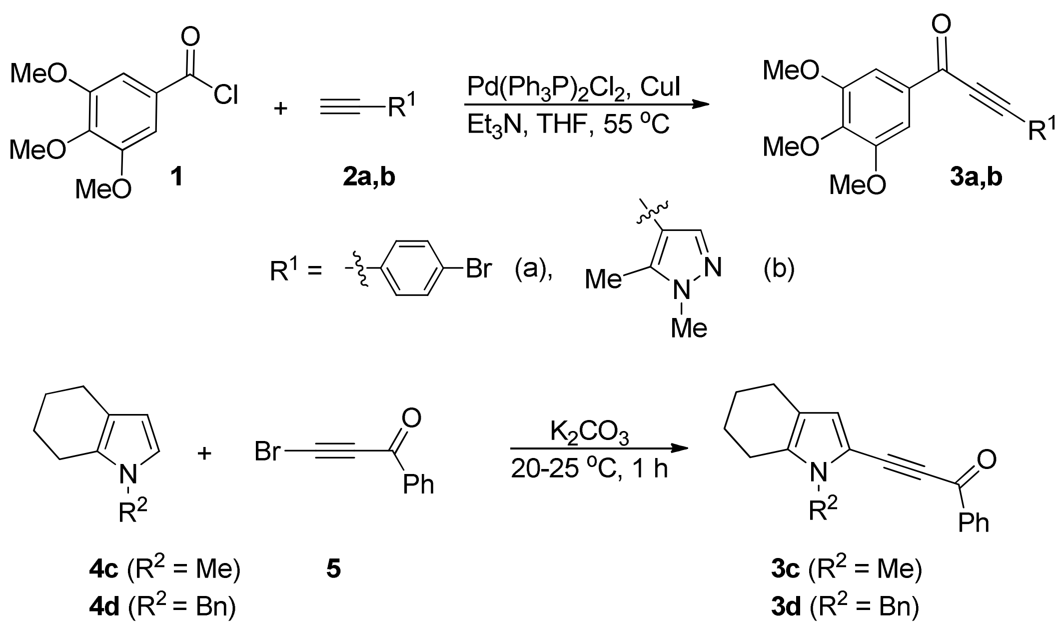
The necessity for a more detailed investigation of this reaction was dictated also by the literature[8] from which it follows that *α*-ketoacetylenes of similar "push-pull" character (due to the +M-effect of the nitrogen atom) can undergo other transformations in the reactions with EDA. For example, it has been reported[9] that 4-dialkylamino-3-butyn-2-ones react with this reagent to furnish 2-(2-hydroxyprop-1-enyl)imidazoline, a product of EDA addition, without elimination of a ketone molecule (Scheme 2).



Scheme 2. Reaction of 4-dialkylamino-3-butyn-2-ones with EDA.

In addition, in the same work it is mentioned that such substrates can react not only with participation of carbon *β*-atom of the triple bond, but also with involvement of the carbonyl group, *i.e.* with the formation of diazepine derivatives.

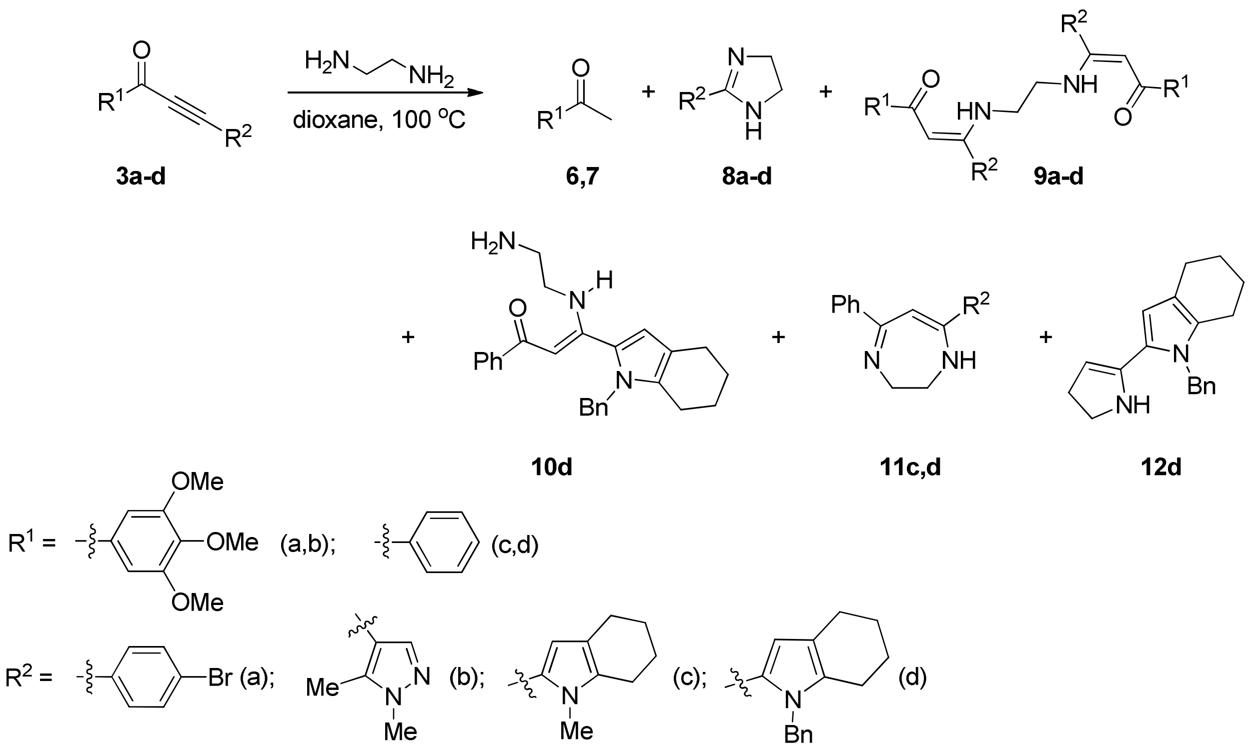
The starting ketoacetylenes **3a** and **3b** were synthesized by a one-stage Pd-catalyzed cross-coupling of 3,4,5-trimethoxybenzoylchloride (**1**) with terminal acetylenes **2a** and **2b**, respectively by a protocol formerly described,[9] and ketoacetylenes **3c** and **3d** were prepared by Pd-free ethynylation of *N*-methyl- and *N*-benzyl-4,5,6,7-tetrahydroindoles **4c** and **4d**, respectively with benzoylbromoacetylene (**5**) on K_2CO_3 via a recently discovered cross-coupling reaction[10] (Scheme 3).



Scheme 3. Two approaches to the preparation of ketoalkynes **3a-d**.

The reaction of *α*-ketoacetylenes **3a-d** with EDA was carried out by heating under reflux their equimolar mixture in dioxane until disappearance of the starting acetylene (TLC-control). As expected, in the case of ketoacetylene **3a** with the two acceptor substituents, the reaction was the fastest (2 h). Pyrazole derivative **3b** turned out to be less reactive (requiring 28 h) due to the +M-effect of the pyrrole nitrogen atom in the initial heterocycle. The most deactivating +M-effect was observed for tetrahydroindole derivatives **3c** and **3d** (reaction time was 40 h). The increase in reaction time may also be attributed to steric hindrance.

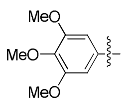
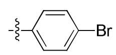
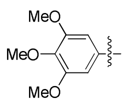
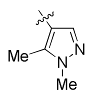
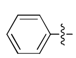
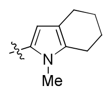
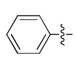
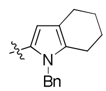
As a whole, the process comprises a series of consecutive transformations. The composition and structure of the formed (detected by GCMS, Table 1) and isolated products allow the previously proposed sequence of cascade reactions (Scheme 1)[7] to be confirmed. Namely, the process involves the intermolecular addition of amine to give monoadducts $A1_{inter}$, the subsequent intramolecular Michael-addition (5-*exo-trig*-cyclization) and fragmentation of intramolecular cyclization products $A1_{intra}$ (retro-Mannich) to deliver ketones **6** and **7** and 2-substituted imidazolines **8a-d** (Scheme 4). Along with these processes, the intermolecular addition of the free amino group of the $A1_{inter}$ monoadduct to the triple bond of ketoacetylenes **3a-d** gives rise to bisadducts **9a-d**.



Scheme 4. Reaction of ketoacetylenes **3a-d** with EDA in refluxing dioxane.

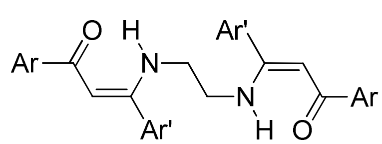
It should be emphasized that the composition of products recorded by GCMS (Table 1) and preparatively isolated products is different: In all the reaction mixtures analyzed by GCMS, the compounds **9a-d**, the products of addition of ketoacetylenes **3a-d** to EDA were not detected. Presumably, this was attributed to the low volatility of these higher molecular weight adducts under the chromatographic conditions. Nevertheless, adducts **9a-d** have been isolated and characterized (see Experimental Section).

Table 1. The products of reaction between ketoacetylenes **3a-d** and EDA according to chromatography-mass spectroscopy data

R^1	R^2	Azepine **11** (%)	Ketone **6,7** (%)	Imidazoline **8a-d** (%)
		-	**6** (52)	**8a** (31)
		-	**6** (58)	**8b** (30)
		**11c** (8)	**7** (11)	**8c** (65)
		**11d** (14)	**7** (15)	**8d** (50)

On the other hand, it was shown that upon recording the GCMS of compound **10d**, splitting of the $A1_{inter}$ monoadduct took place (owing to the high temperature – 300 °C). These results are in agreement with our previous finding,[7] which support that an increase in temperature during the reaction between ketoacetylenes and EDA even by 25 °C (from 100 °C to 125 °C) leads to significantly larger yields of monoadduct $A1_{inter}$ fragmentation products (by 20-40%).

In the IR spectra of compounds **9a-d** the carbonyl stretching vibration *ν*(C=O) was shifted to 1591-1595 cm^{-1} (in the starting ketoacetylenes this band was observed at 1608-1635 cm^{-1}) due to hydrogen bond formation N-H···O=C. This is in good agreement with data previously reported,[11] where the authors explained a similar shift by the chelation of the C=O bond (Scheme 5).



Scheme 5. Formation of hydrogen bonds in **9a-d**.

The low content of acetophenone **7** may be attributed to its high volatility. Apparently, the losses of low-boiling acetophenone occur during the sample preparation (in the course of solvents distillation in vacuum) for MS recording. In addition, separation of the reaction mixture leads to the problems with isolation of acetophenone **7**. Therefore a method for the preparation of acetophenone 2,4-dinitrophenylhydrazone was employed for identification of acetophenone **7**.

The results of investigations have revealed the peculiar behavior of the tetrahydroindole derivatives **3c** and **3d**. Besides the expected fragmentation products (acetophenone **7** and imidazoline **8c**), azepines **11c** and **11d** were detected for the first time. Additionally, compound **11d** was isolated in preparative yield (13%; Scheme 6).

We propose that the diazepines **11c** and **11d** from the tetrahydroindole derivatives **3c** and **3d**, respectively, can be formed by either of two routes: Addition of EDA to the acetylene carbon *β* to the carbonyl affords the monoadducts **10c** and **10d**, respectively that subsequently undergo intramolecular cyclodehydration at the carbonyl or EDA initially adds at the carbonyl group to give Schiff bases **11′c** and **11′d**, respectively that then undergo an intramolecular ring closure on the acetylene *β*-carbon (Scheme 6).

Moreover, for benzyl derivative **3d** formation of imidazoline **8d** is not practically realized. The fragmentation products, ketone **7** and imidazoline **8d**, are formed under the conditions of mass spectrum recording (the increased temperature).

Indeed, when the reaction of ketone **3d** was carried out with three-fold excess EDA, mainly monoadduct **10d** was isolated in 70% yield. The products of the triple bond cleavage, acetophenone and imidazoline **8d** as well as diazepine **11d** were not found in the reaction mixture (TLC). At the same time, when of the GCMS of this sample was recorded, the reaction mixture contained acetophenone **7** (6%), imidazoline **8d** (24%) and diazepine **11d** (35%).

Compound **10d** was isolated as the *Z*-isomer. The *Z*-configuration of the double bond was assigned by correlations of ^{2}H (5.72)-^{12}H (5.15) in the NOESY spectrum (Figure 1).

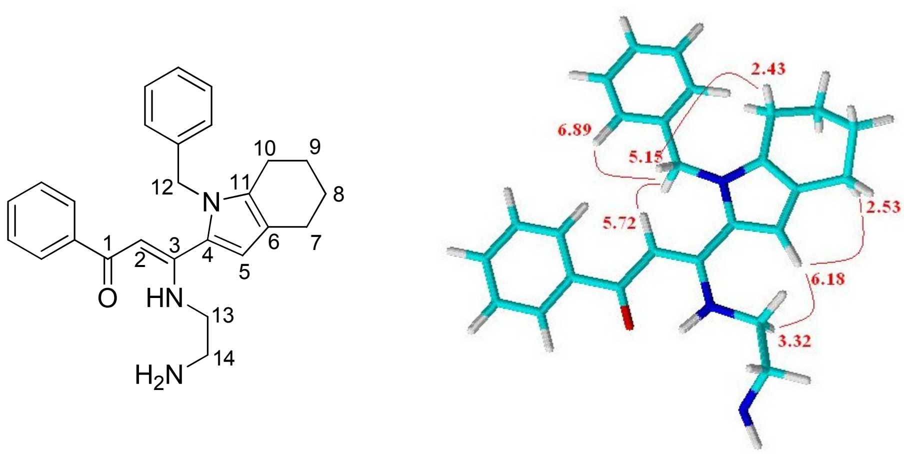
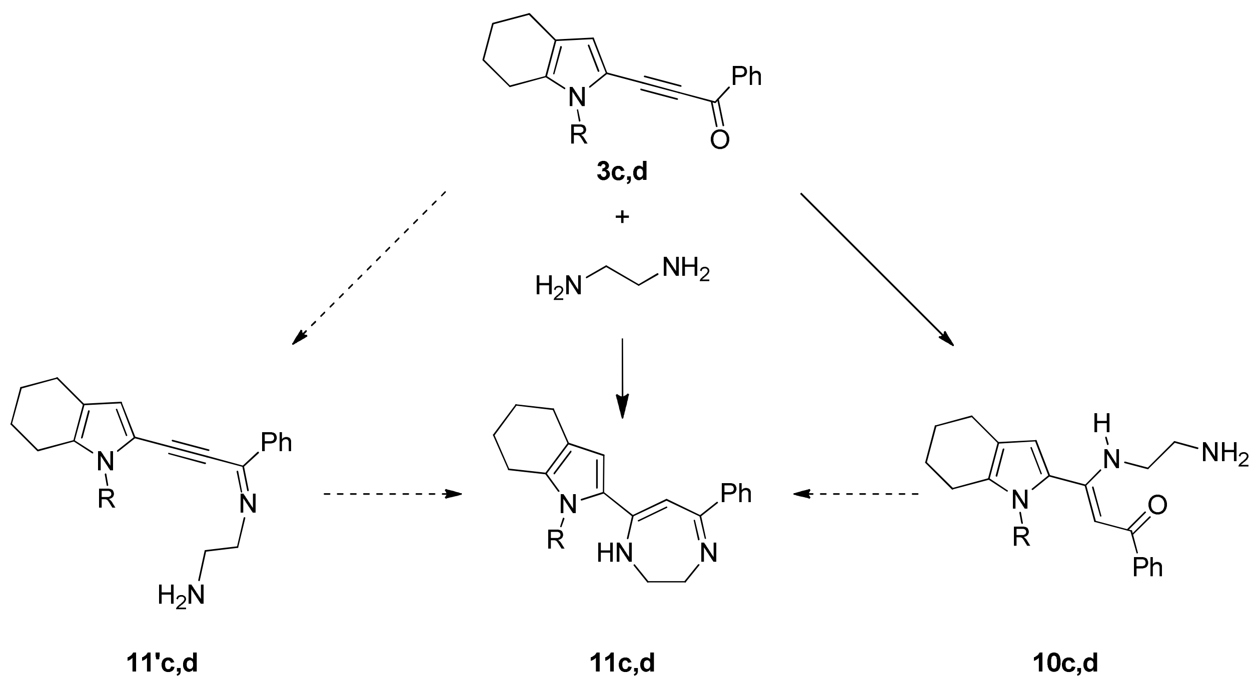


Figure 1. Determination of *Z*-configuration of compound **10d** by the NOESY spectrum.

The COSY spectrum of compound **10d** showed cross-peaks between 3.32 ($^{13}CH_2$) and 11.37 (NH), 3.32 ($^{13}CH_2$) and 2.71 ($^{14}CH_2$), 2.53 ($^{7}CH_2$) and 1.72 ($^{8}CH_2$), 1.77 ($^{9}CH_2$) and 2.43 ($^{10}CH_2$). In the HMBC spectrum (J_{CH} 7 Hz), a peak at 186.9 (^{1}CO) correlates with the peaks at

5.72 (^{2}CH) and 7.55 (CH_{Ar}), peak at 158.2 (^{3}C) with peaks at 5.72 (^{2}CH) and 3.32 ($^{13}CH_2$), peak at 47.4 ($^{12}CH_2$) with peaks at 6.89 (CH_{Ar}), peak at 47.7 ($^{13}CH_2$) with peaks at 2.71 ($^{14}CH_2$), peak at 125.0 (^{4}C) with peaks at 5.15 ($^{12}CH_2$) and 6.18 (^{5}CH), peak at 132.2 (^{11}C) with peaks at 5.15 ($^{12}CH_2$) and 6.18 (^{5}CH) and 2.43 ($^{10}CH_2$), peak at 118.1 (^{6}C) with peaks at 6.18 (^{5}CH) and 2.53 ($^7CH_2$).

The structure of products **11c** and **11d** can be corresponded to both open-chained **11'c** and **11'd** and cyclic Schiff base **11c** and **11d** (Scheme 6). The spectral data unambiguously indicate the cyclic structure of this compound. In the IR spectrum of the isolated benzyl derivative characteristic signals of the terminal amino group (for **11'c,d** and **10c,d**) and triple bond (for **11'c** and **11'd**) in the region of 2200 cm^{-1} are absent. At the same time, in the ^{1}H NMR spectrum of this compound, a singlet of olefinic fragment in the diazepine moiety appears at 5.33 ppm. In addition typical signals of carbon atoms of the triple bond in ^{13}C NMR (in range 87 - 92 ppm) are absent.



Scheme 6. Possible pathways for the formation of dihydrodiazepines **11c** and **11d**.

Another peculiarity of the reaction of tetrahydroindole derivative **3d** with EDA is the formation of 1-benzyl-2-(4,5-dihydro-1*H*-pyrrol-2-yl)-4,5,6,7-tetrahydro-1*H*-indole **12d** (5%) the structure of which was supported by spectral data. However, we have yet to propose a rational explanation for the formation of the dihydropyrrole **12d** and this is currently under investigation.

Conclusions

In conclusion, the generality of α-ketoacetylene cleavage under the action of EDA, leading to the corresponding 2-substituted imidazolines and arylmethylketones, is confirmed. Peculiarities of the substrates bearing strong donor substituents in the acetylene counterpart of the molecule were found. These peculiarities are responsible for alternative directions of the reaction, *viz.* formation of the azepine and products of its rearrangement – 1(*R*)-2-(4,5-dihydro-1*H*-pyrrol-2-yl)-4,5,6,7-tetrahydro-1*H*-indole.

Experimental Section

General. Melting points were determined with a Kofler apparatus. IR-spectra were recorded in KBr pellets on a Vector 22 instrument. NMR spectra were recorded on a Bruker AV-400 spectrometer at 400 (^{1}H) and 100 MHz (^{13}C) and Bruker AV-600 spectrometer at 600 MHz (^{1}H) and 150 MHz (^{13}C) in $CDCl_3$ and DMSO-d_6. Chemical shifts were given in (δ ppm) relative to the residue signals of $CHCl_3$ (δ_H 7.24 ppm and δ_C 76.90 ppm) and DMSO-d_6 (δ_H 2.50 ppm and δ_C 39.50 ppm). GCMS analysis were performed on a Hewlett-Packard instrument, which included a gas chromatograph HP 5890 series II and mass-selective detector HP 5971 (70 eV). Mass spectra (HRMS) were measured on a Thermo Scientific DFS (Double Focusing Sector Mass Spectrometer) Thermo Electron Corporation, 70 eV and on a Micro TOF-Q (Bruker Daltonics) spectrometer. Column chromatography was performed on SiO_2 (Merck 60, 0.063-0.2 mm). Analytical TLC was performed with Merck silica gel 60 F_{254} plates. $Pd(Ph_3P)_2Cl_2$, methyl-3-butyn-2-ol, THF, Et_3N, EDA were commercially available (Sigma-Aldrich) reagents.

4-Ethynylbromobenzene (**2a**) was obtained with yield 65% by retro-Favorsky reaction of 4-(4-bromophenyl)-2-methylbut-3-yn-2-ol. Mp 59-60 °C (hexane), lit. mp 63 °C.[12]
1,5-Dimethyl-4-ethynylpyrazole (**2b**) was obtained with yield 66% by retro-Favorsky reaction of 4-(1,5-dimethyl-1*H*-pyrazol-4-yl)-2-methylbut-3-yn-2-ol. Mp 62-63 °C, lit. mp 63-63.5 °C.[13]

Synthesis of ketoacetylenes 3a-d
3-(4-Bromophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (3a). A mixture of $Pd(Ph_3P)_2Cl_2$ (0.130 g, 0.186 mmol) and CuI (0.08 g, 0.42 mmol) in THF (30 mL) was stirred in the argon atmosphere for 10 min. Then triethylamine (5 mL), 3,4,5-trimethoxybenzoyl chloride (**1**) (2.3 g, 10 mmol), and 4-ethynylbromobenzene (**2a**) (1.8 g, 10 mmol) were added. The reaction mixture was stirred at 55 °C for 11 h. Solvents were evaporated, and the residue was purified on the column with SiO_2 (toluene) to give 1.76 g (47%) of acetylene **3a**, mp 160-162 °C. IR (KBr, ν, cm^{-1}): 1635 (C=O); 2204 (C≡C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 9H), 7.47 (s, 2H), 7.50-7.52 (m, 2H), 7.56-7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.14 (3,5-OCH_3),

60.91, 87.42, 91.31, 106.73, 118.88, 125.45, 131.79, 132.01, 134.06, 143.58, 152.94, 176.45. HRMS, found: *m/z* 374.0151 $[M]^+$. $C_{18}H_{15}BrO_4$. Calcd: M 374.0148.

3-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-1-(3,4,5-trimethoxy-phenyl)prop-2-yn-1-one (3b). A mixture of $Pd(Ph_3P)_2Cl_2$ (65 mg, 0.093 mmol) and CuI (40 mg, 0.211 mmol) in THF (20 mL) was stirred in the argon atmosphere for 10 min. Then triethylamine (5 mL), 3,4,5-trimethoxybenzoyl chloride (**1**) (1.15 g, 5 mmol) and 1,5-dimethyl-4-ethynylpyrazole (**2b**) (0.60 g, 5 mmol) were added successively. The reaction mixture was stirred at 55 °C for 5 h. Solvents were evaporated, and the residue was purified on the column with SiO_2 (toluene) to give 1.1 g (70%) of acetylene **3b**, mp 222-223 °C. IR (KBr, ν, cm^{-1}): 1624 (C=O); 2183 (C≡C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.83 (s, 3H), 3.94 (s, 9H), 7.46 (s, 2H), 7.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.35, 36.67, 56.11 (3,5-OMe), 60.88, 87.22, 91.45, 99.68, 106.60, 132.18, 142.10, 143.20, 144.51, 152.92, 176.52. HRMS, found: *m/z* 314.1260 $[M]^+$. $C_{17}H_{18}N_2O_4$. Calcd: M 314.1261

2-Benzoylethynyl-1-methyl-4,5,6,7-tetrahydroindole (3c). Equimolar amounts of 1-methyl-4,5,6,7-terahydroindole (0.135 g, 1 mmol) and benzoylbromoacetylene (0.209 g, 1 mmol) were grinded together at r.t. with a 10-fold amount (3.44 g) K_2CO_3 in a china mortar and pestle for 10 min. The reaction mixture self-heated (5-8 °C) and within 10 min turned from yellow to orange-brown. After 1 h the reaction mixture was placed on the column with Al_2O_3 and eluted with *n*-hexane to afford pure 0.179 g (68%) of acetylene **3c**, mp 116-117 °C. Physico-chemical and spectral characteristics of acetylene **3c** are given in ref. 14.

2-Benzoylethynyl-1-benzyl-4,5,6,7-tetrahydroindole (3d). Equimolar amounts of 1-benzyl-4,5,6,7-terahydroindole (0.211 g, 1 mmol) and benzoylbromoacetylene (0.209 g, 1 mmol) were ground together at r.t. with a 10-fold amount (4.20 g) K_2CO_3 in a china mortar and pestle for 10 min. The reaction mixture self-heated (5-8 °C) and within 10 min turned from yellow to orange-brown. After 1 h the reaction mixture was placed on the column with Al_2O_3 and eluted with *n*-hexane to afford pure 0.241 g (71%) of acetylene **3d**, mp 106-107 °C. Physico-chemical and spectral characteristics of acetylene **3d** are given in ref. 14.

The reaction of 3-(4-bromophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (3a) with EDA. The solution of α-ketoacetylene 3a (0.752 g, 2 mmol) and EDA (0.120 g, 2 mmol) in 1,4-dioxane (7 mL) was boiled for 2 h. Then dioxane was removed *in vacuo* and the residue was fractioned on a column with SiO_2 [hexane-toluene (1:1), toluene, toluene-EtOAc (1:1), EtOAc, EtOH] to afford.

First fraction [eluent – hexane-toluene (1:1), toluene] – 1-(3,4,5-trimethoxyphenyl)ethanone (**6**), 0.150 g (35%), mp 77-79 °C, lit. mp 78-79 °C.[15]

Second fraction (eluent – toluene-EtOAc, 1:1) – (2Z,2'Z)-3,3'-[ethane-1,2-diylbis(azanediyl)]-bis[3-(4-bromophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one] (**9a**), 65 mg (8%), mp 240-242 °C. IR (KBr, ν, cm^{-1}): 1593 (C=O chelated); 3433 (NH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (m, 2H), 3.88 (s, 9H), 5.63 (s, 1H), 7.10 (s, 2H), 7.13 (d, *J* 8.3 Hz, 2H), 7.53 (d, *J* 8.3 Hz, 2H), 11.16 (br. s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.02, 56.11, 60.80, 93.92, 104.24, 123.86, 129.19, 131.92, 133.70, 135.01, 140.76, 152.87, 165.07, 187.78. HRMS, found: *m/z* 613.0329

$[M]^+$. $C_{28}H_{27}O_4N_2Br_2$. Calcd: M 613.0332; found: *m/z* 195.0651 $[M]^+$. $C_{10}H_{11}O_4$. Calcd: M 195.0652. It was not possible to measure of the exact mass of a molecular ion because the isotope peaks of a molecular ion have low intensity, therefore the value of the molecular ion was calculated as the sum of peaks-splinters (Calcd: M 808.0989, $C_{38}H_{38}O_8N_2Br_2$).

Third fraction (eluent – EtOAc, EtOH) – 2-(4-bromophenyl)-4,5-dihydro-1*H*-imidazole (**8a**), 0.115 g (26%), mp 175-177 °C, lit. mp 177-177.5 °C.[16]

The reaction of 3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (3b) with EDA. The solution of α-ketoacetylene **3b** (0.628 g, 2 mmol) and EDA (0.120 g, 2 mmol) in 1,4-dioxane (7 mL) was boiled for 28 h. Then dioxane was removed in vacuo and a residue was fractioned on the column with SiO_2 [hexane-toluene (1:1), toluene, toluene-EtOAc (1:1), EtOAc, EtOH] to afford:

First fraction [eluent – hexane-toluene (1:1), toluene] – 1-(3,4,5-trimethoxyphenyl)ethanone (**6**), 190 mg (45%).

Second fraction (eluent – toluene-EtOAc, 1:1) – (2Z,2'Z)-3,3'-[ethane-1,2-diylbis(azanediyl)]-bis[3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one] (**9b**), 50 mg (7%), mp 86-88 °C. IR (KBr, ν, cm^{-1}): 1591 (C=O chelated); 3437 (NH). ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.42 (m, 2H), 3.86 (s, 3H), 3.89 (s, 9H), 5.61 (s, 1H), 7.10 (s, 2H), 7.40 (s, 1H), 11.29 (br.s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.24, 36.52, 44.83, 56.05, 60.78, 94.32, 104.12, 114.21, 135.42, 137.25, 137.40, 140.43, 152.79, 159.25, 187.31. HRMS, found: *m/z* 687.3112 $[M-H]^+$. $C_{36}H_{43}O_8N_6$. Calcd: M 688.3215.

Third fraction (eluent – EtOAc, EtOH) – the solution containing (TLC-control) 4-(4,5-dihydro-1*H*-imidazol-2-yl)-1,5-dimethyl-1*H*-pyrazole (90 mg). The residue after removing the solvents was dissolved in diethyl ether and dry gas HCl was passed through this solution. The resulting precipitate was washed with diethyl ether, dried over P_2O_5 to afford 4-(4,5-dihydro-1*H*-imidazol-2-yl)-1,5-dimethyl-1*H*-pyrazole hydrochloride (**8b·HCl**), 110 mg (27%), mp 150-152 °C. IR (KBr, ν, cm^{-1}): br. region 2979-3080 (NH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.64 (s, 2H), 3.72 (s, 3H), 3.92 (s, 2H), 7.34 (s, 1H), 9.92 (br. s, 1H). HRMS, found: *m/z* 164.1054 $[M-HCl]^+$. $C_8H_{12}N_4$. Calcd: M 200.0823.

The reaction of 2-benzoylethynyl-*N*-methyl-4,5,6,7-tetrahydroindole (3c) with EDA. The solution of α-ketoacetylene **3c** (0.526 g, 2 mmol) and EDA (0.120 g, 2 mmol) in 1,4-dioxane (7 mL) was boiled for 40 h. Then dioxane was removed in vacuo and a residue was fractioned on the column with SiO_2 [hexane-toluene (1:1), toluene, toluene-EtOAc (1:1), EtOAc, EtOH] to afford:

First fraction [eluent – hexane-toluene (1:1), toluene] – this fraction was treated with ethanolic solution of 2,4-dinitrophenylhydrazine to afford 2,4-dinitrophenylhydrazone acetophenone, 60 mg (10%), mp 248-250 °C, lit mp 247-248 °C.[17]

Second fraction (eluent – toluene-EtOAc, 1:1) – (2Z,2'Z)-3,3'-[ethane-1,2-diylbis(azanediyl)]-bis(3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-one) (**9c**), 50 mg (8%), mp 72-74 °C. IR (KBr, ν, cm^{-1}): 1594 (C=O chelated); 3431 (NH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.77-1.88 (m, 4H), 2.50-2.56 (m, 4H), 3.45 (s, 3H), 3.49-3.51 (m, 2H), 5.78 (s, 1H), 6.05 (s, 1H), 7.37-7.43 (m, 3H), 7.84-7.86 (m, 2H), 11.20 (br. s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.10, 22.84, 22.94, 23.28, 31.09, 45.18, 94.74, 110.20, 117.92, 124.78, 126.87, 128.07, 130.56, 132.28, 140.15, 158.45, 187.82. HRMS, found: *m/z* 586.3307 $[M]^+$. $C_{38}H_{42}N_4O_2$. Calcd: M 586.3302.

Third fraction (eluent – EtOAc, EtOH) – 2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-methyl-4,5,6,7-tetrahydro-1*H*-indole (**8c**), 120 mg (29%), mp 138-140 °C. IR (KBr, *ν*, cm^{-1}): 3428 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, 97.5 °C) δ 1.63-1.81 (m, 4H), 2.39-2.53 (m, 4H), 3.51 (s, 4H), 3.75 (s, 3H), 6.29 (s, 1H). HRMS, found: *m/z* 202.1336 $[M-H]^+$. $C_{12}H_{16}N_3$. Calcd: M 203.1417.

The reaction of 2-benzoylethynyl-*N*-benzyl-4,5,6,7-tetrahydroindole (3d) with EDA. A. The solution of *α*-ketoacetylene **3d** (0.678 g, 2 mmol) and EDA (0.120 g, 2 mmol) in 1,4-dioxane (7 mL) was boiled for 40 h. Then dioxane was removed in vacuo and a residue was fractioned on the column with SiO_2 (hexane-toluene (1:1), toluene, toluene-EtOAc (1:1), EtOAc, EtOH) to afford:

First fraction (eluent – hexane-toluene (1:1), toluene) – this fraction was treated with ethanolic solution of 2,4-dinitrophenylhydrazine to afford 2,4-dinitrophenylhydrazone acetophenone, 30 mg (5%), mp 246-248 °C, lit. mp 247-248 °C.[17]

Second fraction (eluent – toluene-EtOAc, 1:1) – (2Z,2'Z)-3,3'-[ethane-1,2-diylbis(azanediyl)]-bis[3-(1-benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-one] (**9d**), 45 mg (6%), mp 81-83 °C. IR (KBr, *ν*, cm^{-1}): 1595 (C=O chelated); 3431 (NH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.85 (m, 4H), 2.43-2.55 (m, 4H), 3.34 (br. s, 2H), 5.08 (s, 2H), 5.67 (s, 1H), 6.09 (s, 1H), 6.84 (d, *J* 8.32 Hz, 2H), 7.26-7.36 (m, 6H), 7.49 (d, *J* 8.32 Hz, 2H), 11.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.22, 22.93, 23.00, 23.35, 45.14, 47.66, 94.31, 111.21, 118.42, 124.80, 125.75, 126.83, 126.93, 127.92, 128.65, 130.40, 132.49, 138.51, 139.96, 158.19, 187.39. HRMS, found: *m/z* 738.3913 $[M]^+$. $C_{50}H_{50}N_4O_2$. Calcd: M 738.3928.

Third fraction (eluent – toluene-EtOAc, 1:1) – (*Z*)-3-(2-aminoethylamino)-3-(1-benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-one (**10d**), 320 mg (40%) as a yellow oil. IR (KBr, *ν*, cm^{-1}): 1593 (C=O chelated); 3406 (NH_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.72 (m, 2H, $^8CH_2$), 1.77 (m, 2H, $^9CH_2$), 2.43 (t, $^3J_{10H\text{-}9H}$ 5.9 Hz, 2H, $^{10}CH_2$), 2.53 (t, $^3J_{7H\text{-}8H}$ 6.0 Hz, 2H, $^7CH_2$), 2.71 (t, $^3J_{14H\text{-}13H}$ 6.0 Hz, 2H, $^{14}CH_2$), 3.32 (dt, $^3J_{13H\text{-}14H}$ 6.0 Hz, $^3J_{13H\text{-}NH}$ 5.9 Hz, 2H, $^{13}CH_2$), 5.15 (s, 2H, $^{12}CH_2$), 5.72 (s, 1H, ^{2}CH), 6.18 (s, 1H, ^{5}CH), 6.89 (d, ^3J 7.4 Hz, 2H, CH_{Ar}), 7.15-7.34 (m, 6H, CH_{Ar}), 7.55 (dd, ^3J 8.4 Hz, ^4J 1.4 Hz, 2H, CH_{Ar}), 11.37 (t, $^3J_{13H\text{-}NH}$ 5.9 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.96 ($^{10}CH_2$), 22.67 ($^7CH_2$), 22.76 ($^9CH_2$), 23.11 ($^8CH_2$), 42.02 ($^{14}CH_2$), 47.43 ($^{12}CH_2$), 47.72 ($^{13}CH_2$), 93.39 (^{2}CH), 111.22 (^{5}CH), 118.06 (^{6}C), 124.98 (^{4}C), 125.53 (C_{Ar}), 126.52 (C_{Ar}), 126.78 (C_{Ar}), 127.68 (C_{Ar}), 128.40 (C_{Ar}), 130.07 (C_{Ar}), 132.20 (^{11}C), 138.15 (C_{Ar}), 139.86 (C_{Ar}), 158.18 (^{3}C), 186.86 (^{1}CO). HRMS, found: *m/z* 400.2355 $[M+H]^+$. $C_{26}H_{30}N_3O$. Calcd: M 399.2311.

Fourth fraction (eluent – EtOAc) – 1-benzyl-2-[(1*E*,5*Z*)-7-phenyl-3,4-dihydro-2*H*-1,4-diazepin-5-yl)-4,5,6,7-tetrahydro-1*H*-indole (**11d**), 0.100 g (13%), mp 88-90 °C. IR (KBr, *ν*, cm^{-1}): 1658 (C=N); 3419 (NH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.79 (m, 4H), 2.45-2.51 (m, 4H), 3.62-3.73 (m, 4H), 5.22 (s, 2H), 5.33 (s, 1H), 6.62 (s, 1H), 6.81 (d, *J* 8.32 Hz, 2H), 7.19-7.42 (m, 8H), 8.97-9.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.51, 22.68, 22.81, 23.19, 48.28, 49.18, 50.20, 89.95, 116.55, 120.40, 125.50, 127.46, 127.69, 128.96, 131.45, 136.21, 137.75, 138.78, 156.69, 164.09. HRMS, found: *m/z* 380.2124 $[M-H]^+$. $C_{26}H_{26}N_3$. Calcd: M 381.2199.

Fifth fraction (eluent – EtOAc) – 1-benzyl-2-(4,5-dihydro-1*H*-pyrrol-2-yl)-4,5,6,7-tetrahydro-1*H*-indole (**12d**), 0.030 g (5%), mp 76-78 °C (benzene). IR (KBr, *v*, cm^{-1}): 3400 (NH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74-1.78 (m, 4H), 2.45-2.53 (m, 4H), 3.34-3.46 (m, 4H), 5.18 (s, 2H), 5.78 (s, 1H), 6.21 (s, 1H), 7.36-7.59 (m, 5H), 11.22 (br.s, 1H). HRMS, found: *m/z* 277.1696 $[M-H]^+$. $C_{19}H_{21}N_2$. Calcd: M 278.1783.

B. The solution of α-ketoacetylene **3d** (0.339 g, 1 mmol) and EDA (0.180 g, 3 mmol) in 1,4-dioxane (5mL) was boiled for 5 h. Then dioxane was removed in vacuo. The crude product was purified on SiO_2 (toluene-EtOAc, 1:1) to give 0.279 g (70%) of (*Z*)-3-(2-aminoethylamino)-3-(1-benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-one (**10d**) as a yellow oil (spectral data see above).

Acknowledgements

This work was supported by RFBR (grant №13-03-00129a and №13-03-911550-NNSFC), the Russian Academy of Sciences (grant 5.9.3, 2014), the Ministry of Education and Science of the Russian Federation and the Chemical Service Centre of SB RAS.

References

1. *Acetylene Chemistry: Chemistry, Biology and Material Science*, Eds. Diederich, F.; Stang, P. J.; Tykwinski, R. R. Wiley-VCH, Weinheim, 2005.
2. Shi, F.; Luo, S.-W.; Tao, Z. L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett*. **2011**, *13*, 4680.
http://dx.doi.org/10.1021/ol201898x
3. Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L. Feng, X. *Angew. Chem. Internat. Ed*. **2012**, *51*, 2776.
http://dx.doi.org/10.1002/anie.201109130
4. Li, H.-F.; Xu, X.-L.; Yang, J.-Y.; Xie, X.; Huang, H.; Li, Y.-Z. *Tetrahedron Lett*. **2011**, *52*, 530.
http://dx.doi.org/10.1016/j.tetlet.2010.11.106
5. Gilmore, K.; Alabugin, I. V. *Chem. Rev*. **2011**, *111*, 6513.
http://dx.doi.org/10.1021/cr200164y
6. Davydova, M. P.; Vasilevsky S. F.; Tolstikov, G. A. *Russ. Chem. Bull*. **2011**, *60*, 188.
7. Roy, S.; Davydova, M. P.; Pal, R.; Gilmore, K.; Tolstikov, G. A.; Vasilevsky S. F.; Alabugin, I. V. *J. Org. Chem.* **2011**, *76*, 7482.

http://dx.doi.org/10.1021/jo201259j

8. Ostroumov, I. G.; Tsilko, A. E.; Maretina I. A.; Petrov A. A. *J. Org. Chem. USSR* (Engl. Transl.), **1988**, *24*, 1165.
9. Karpov, A. S.; Muller, T. J. J. *Org. Lett*. **2003**, *5*, 3451. http://dx.doi.org/10.1021/ol035212q
10. Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Ushakov, I. A.; Petrova, O. V.; Tarasova, O. A.;Volkova, K. A.; Mikhaleva, A. I. *Synthesis* **2007**, 447. http://dx.doi.org/10.1055/s-2007-965884
11. Basyouni, M. N.; Fouli, F. A. *Acta Chim. Acad. Sci. Hung*. **1980**, *105*, 235.
12. Matveeva, E. D.; Erin, A. S.; Kurts, A. L. *Zh. Org. Khim.* **1997**, *33*, 1141.
13. Vasilevsky, S. F.; Sinyakov, A. N.; Shvartsberg, M. S.; Kotlyarevsky, I. L. *Russ. Chem. Bull.* **1976**, *10*, 2134.
14. Sobenina, L. N.; Tomilin, D. N.; Petrova, O. V.; Gulia, N.; Osowska, K.; Szafert, S.; Mikhaleva, A. I.; Trofimov, B. A. *Russ. J. Org. Chem*. **2010**, *46*, 1373.
15. Harding, V. J. *J. Chem. Soc. Trans*. **1914**, *105*, 2790. http://dx.doi.org/10.1039/CT9140502790
16. Ishihara, M.; Togo, H. *Synthesis* **2007**, 1939. http://dx.doi.org/10.1055/s-2007-983726
17. Jones, L. A.; Mueller, N. L. *J. Org. Chem.* **1962**, *27*, 2356. http://dx.doi.org/10.1021/jo01054a016

