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(Aza)indolizines and ethyl propiolate: [8+2] and [1,10] cyclizations

Eugene V. Babaev[1]*, Ivan A. Shadrin[1], Viktor B. Rybakov[1]

[1] *Lomonosov Moscow State University, 1 Leninskie Gory, Moscow 119991, Russia; e-mail: babaev@org.chem.msu.ru*

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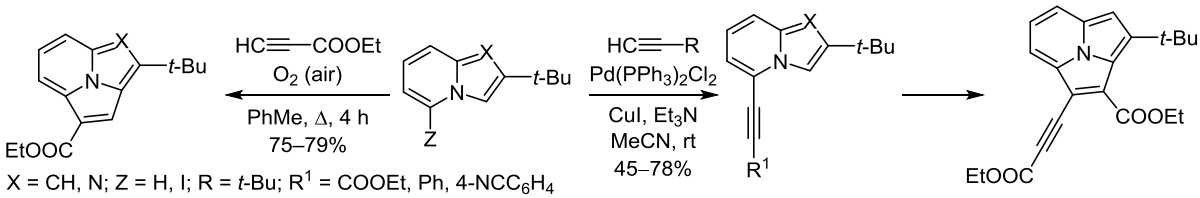


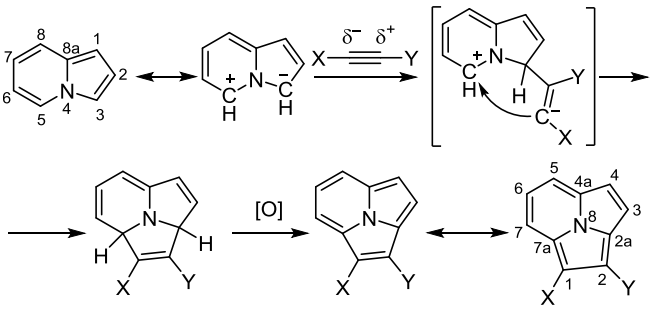
(Aza)indolizines reacted with ethyl propiolate regioselectively forming (aza)[2.2.3]cyclazines. The Sonogashira reaction of 5-iodo(aza)-indolizines and acetylenes led to 5-ethynyl(aza)indolizines. In the case of indolizine derivative the by-product was ethynylcyclazine. The structures of [2.2.3]cyclazines were proved by X-ray structural analysis.

Keywords: imidazo[1,2-*a*]pyridine, indolizine, [8+2] cycloaddition, Sonogashira reaction.

Indolizine, a 10π-electron conjugated system, shows a behavior typical of aromatic systems. In spite of this, it has significant alternations of the bond lengths around the ring system, and cycloaddition of various electron-deficient dienophiles (alkenes and acetylenes) leading to derivatives of pyrrolo[2,1,5-*cd*]indolizine (also called [2.2.3]cyclazine) is well studied (Scheme 1).[1] The mechanism of these reactions was frequently regarded as a rare example of [8+2] cycloaddition, where the tetraene carbon framework of the bicyclic indolizine scaffold played the role of an 8π-electron fragment.

For many years we were interested in the chemistry of indolizines, and particularly, in the mechanism of their [8+2] cycloaddition.[2] Analysis of literature showed that starting from the pioneering work of Boekelheide[1a] this reaction has been considered regioselective due to the pronounced polarization of the indolizine ring.

Scheme 1. Mechanism of [8+2] cycloaddition to indolizine ring

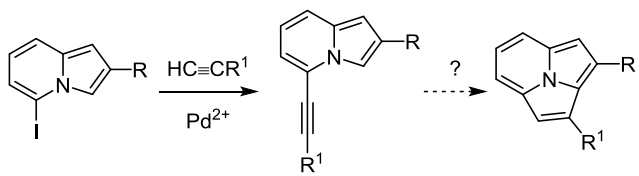


Many alkynes have been involved in this reaction. However, the reactivity of alkyl propiolates, the simplest example of polarized acetylenes, has not been fully characterized in this conversion. Thus, only the reactions between 1,8-cycloalkano-[3a] or bisethylenoindolizines[3b] and alkyl propiolate leading to cyclazines have been described. In all other cases, 1- or 2-alkoxycarbonyl derivatives (X or Y = CO_2R) have been obtained by other methods: intra-[4a] or intermolecular[4b] cyclocondensations or even alternative cycloadditions.[4c] One report on an example of propiolate cycloaddition *via* 3-component Chichibabin reaction to our opinion involved of misprints (cf. structures **4e–i** in the referred article).[4d] Therefore, the first goal of this paper was reinvestigation of [8+2] cycloaddition of indolizine with ethyl propiolate.

Earlier we described the Sonogashira reaction of 5-iodo-indolizines leading to their 5-ethynyl derivatives.[5] The obtained structures have suitable perimeter for allowed [1,10] peri-cyclic cyclization reaction to give [2.2.3]cyclazines (Scheme 2).

No reaction of 5-iodoindolizines with alkyl propiolate has been described, although further cyclization could

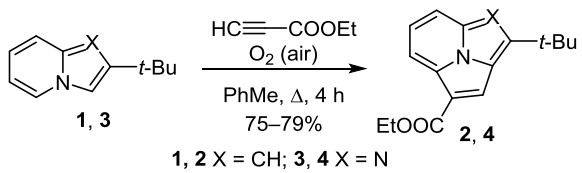
Scheme 2. Used and planned transformations



occur during the action of catalyst or thermal conditions. Therefore, the second goal of this paper was the study of Pd-catalyzed propiolate reaction with iodoindolizine. Finally, we discuss the behavior of 1-aza analogs of indolizines in these reactions.

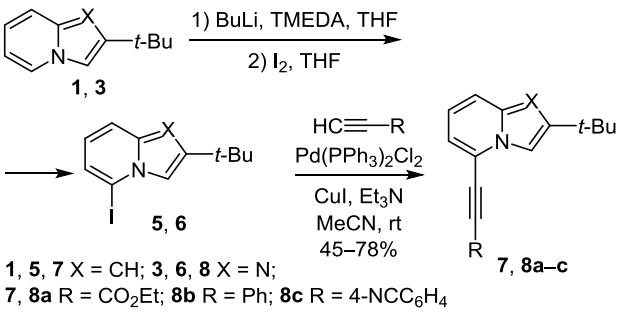
We found that the reaction of 2-*tert*-butylindolizine (**1**) and ethyl propiolate in toluene on heating for 4 h led to the previously unknown structure of pyrrolo[2,1,5-*cd*]indolizine **2** containing an ester group (Scheme 3). It is evident that the reaction proceeded through oxidation by air of the intermediate dihydro structure. The location of the ethoxycarbonyl group at position 1 was proven by X-ray data (Fig. 1). The absence of an isomer with the CO_2Et group at position 2 showed that the cycloaddition reaction was regioselective. As it was evident (see Supplementary information file), product **2** did not show a significant bond alternation in the cyclazine ring, nor was there a marked influence of *tert*-butyl and ethoxycarbonyl groups on the symmetry of the cyclazine ring. In similar reaction 2-*tert*-butylimidazo[1,2-*a*]pyridine **3** was converted into analogous tricyclic structure **4** (Scheme 3) which was assigned according to the mass and NMR spectra. Cyclazines are quite stable crystalline compounds, but quickly decompose in solutions, especially in acidic solvents.

Scheme 3. [8+2] Cycloaddition of (aza)indolizine and ethyl propiolate



In the reaction with BuLi and I_2, indolizine **1** and its aza analog **3** were converted to the corresponding 5-iodo derivatives **5** and **6** (Scheme 4). The previously unknown sequence "metalation–iodination" of imidazopyridine nucleus was demonstrated on the example of compound **3**, the structure of product **6** having been proved by X-ray data (Fig. 2).

Scheme 4. Sonogashira reaction of (aza)indolizines



Further the Sonogashira reaction of 5-iodoindolizine **5** gave 5-ethoxycarbonylethynylindolizine **7** in yield 50% under the action of 0.05 equiv of $Pd(PPh_3)_2Cl_2$ and CuI in acetonitrile at room temperature (Scheme 4). The ethoxycarbonylalkynyl structure of the oily indolizine compound **7** clearly followed from its mass spectra as well as NMR ^1H (appearance of carbethoxy group) and ^{13}C spectra (presence of carbethoxy and ethyne groups). Analogous reaction took place in the case of 5-iodoimidazopyridine **6**. In this case, a series of acetylenes (ethyl propiolate, phenylacetylene, and 4-ethynylbenzonitrile) gave ethynyl derivatives **8a–c** with yields 45–78% (Scheme 4). Strong fluorescence of compounds **8b**,**c** should be mentioned.

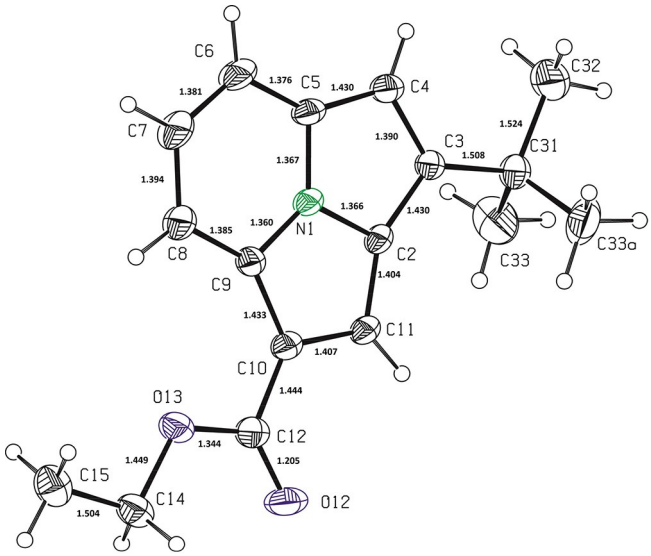


Figure 1. Molecular structure of compound **2** with atoms represented as thermal vibration ellipsoids of 30% probability. Selected bond lengths shown in Å.

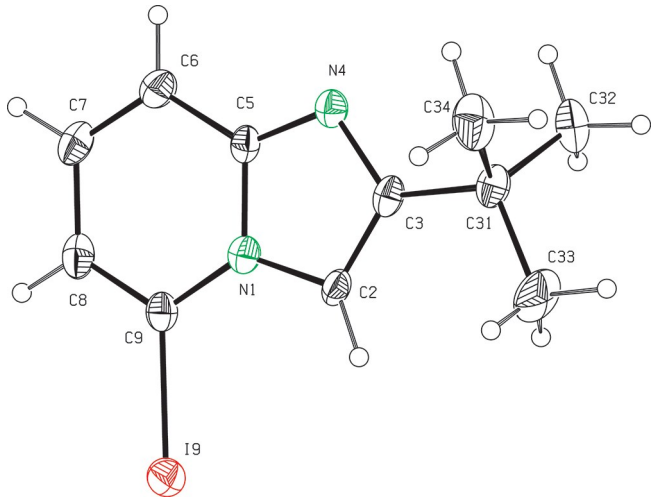
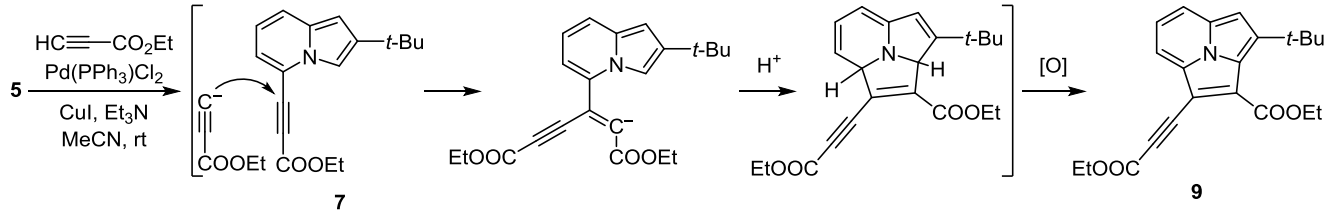


Figure 2. Molecular structure of compound **6** with atoms represented as thermal vibration ellipsoids of 30% probability.

In no cases further cyclization was observed when the ratio of the iodoarene and alkyne was 1:1. However, in the case when the ratio of iodoindolizine **5** to ethyl propiolate was 1:3, the obtained compound was not the product of merely the Sonogashira coupling, but turned out to be cyclazine derivative **9** (Scheme 5). Product **9** was characterized by X-ray structural analysis (Fig. 3). It contained an extra ethyl propiolate unit, and the bond lengths did not alternate within the fused cyclic ring system (see Supplementary information file). We supposed that

Scheme 5. Cycloaddition to 5-iodoindolizine **5** involving 2 equivalents of alkyne



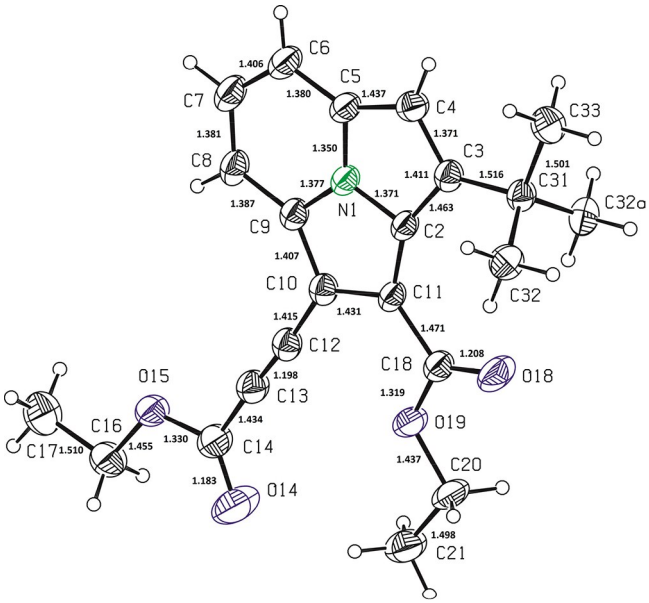


Figure 3. Molecular structure of compound **9** with atoms represented as thermal vibration ellipsoids of 30% probability. Selected bond lengths shown in Å.

such a product could be result of nucleophilic attack of the deprotonated ethyl propiolate on intermediate product **7** and would correspond to its [1,10]-cycloadduct.

As a conclusion, first, we proved the regioselectivity of [8+2] cycloaddition of ethyl propiolate to indolizine and its 1-aza derivative. Second, in the Pd-mediated Sonogashira reaction of 5-iodo(aza)indolizines with acetylenes the alkyne is coupled to position 5. Furthermore, in the case of indolizine, in contrast with azaindolizine, the coupling with an excess of propiolate resulted in further [1,10] cyclization mediated by the nucleophilic attack of acetylene moiety to intermediate alkynylindolizine forming an ethyne derivative of cyclazine.

Experimental

IR spectra were registered on a UR-20 apparatus in petroleum jelly. ^{1}H and ^{13}C HSQC NMR spectra were acquired on a Agilent 400-MR spectrometer (360 and 90 MHz, respectively) in $CDCl_3$ with TMS as internal standard. The NMR signal assignment was done with the help of ^{1}H–^{13}C HSQC experiment. Mass spectra were recorded on an AB Sciex TripleTOF 5600+ MS system with a DuoSprayTM ion source in electrospray ionization mode. Elemental analysis was performed on an Elementar vario MICRO cube CHN-analyzer. Melting points were determined on an Electrothermal IA910 melting point apparatus. Monitoring of the reaction progress was done by TLC on Silufol UV-254 plates, with chloroform as eluent; visualization under UV light (at 254 and 365 nm) or Ehrlich's reagent. Chromatographic purification was done on Merck silica gel (particle size 40–63 μ). Solvents were purified by routine methods.

2-*tert*-Butylindolizine (**1**),[6] 2-*tert*-butylimidazo[1,2-*a*]-pyridine (**3**)[7], and 2-*tert*-butyl-5-iodoindolizine (**5**)[6] were obtained following published methods.

Ethyl 3-*tert*-butylpyrrolo[2,1,5-*cd*]indolizine-1-carboxylate (2). Ethyl prop-2-ynoate (0.255 g, 2.6 mmol, 1.5 equiv) was added to a solution of indolizine **1** (0.294 g, 1.7 mmol) in dry toluene in a round-bottom flask supplied with a condenser and a tube with drying agent ($CaCl_2$). The mixture was then heated and refluxed for 4 h. The reaction was controlled by TLC. After the disappearance of the spot of the initial heterocyclic compound, the mixture was concentrated under the low pressure and separated by column chromatography (hexane–EtOAc, 6:1). Yield 0.368 g (79%), red crystals, mp 132°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48 (3H, s, CH_3); 1.57 (9H, s, $C(CH_3)_3$); 4.43–4.51 (2H, m, CH_2); 7.09 (1H, s, H-4); 7.76–7.79 (2H, m, H-2,6); 8.08–8.10 (1H, m, H-7); 8.30 (1H, d, *J* = 7.0, H-5). ^{13}C NMR spectrum, δ, ppm: 14.4 (CH_3); 29.6 ($C(\underline{C}H_3)_3$); 31.9 ($\underline{C}(CH_3)_3$); 59.8 (CH_2); 101.1 (C-4); 111.3; 114.0 (C-7); 118.6; 119.5 (C-5); 119.8 (C-2); 125.4 (C-6); 125.8; 133.1; 139.3; 167.9 ($\underline{C}O_2Et$). Found, *m/z*: 270.1490 $[M+H]^+$. $C_{17}H_{20}NO_2$. Calculated, *m/z*: 270.1489. Found, %: C 75.89; H 6.98; N 4.96. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20.

Ethyl 2-*tert*-butylimidazo[5,1,2-*cd*]indolizine-4-carboxylate (4) was synthesized analogously to compound **2** from 2-*tert*-butylimidazo[1,2-*a*]pyridine (**3**). Yield 0.202 g (75%), orange crystals, mp 160°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, t, *J* = 7.1, CH_3); 1.64 (9H, s, $C(CH_3)_3$); 4.48 (2H, q, *J* = 7.2, CH_2); 7.91–8.01 (2H, m, H-8,9); 8.13 (1H, s, H-4); 8.26 (1H, d, *J* = 7.3, H-7). ^{13}C NMR spectrum, δ, ppm: 14.4 (CH_3); 30.4 ($C(\underline{C}H_3)_3$); 35.3 ($\underline{C}(CH_3)_3$); 60.4 (CH_2); 110.8 (C-5); 114.5 (C-7); 118.2 (C-4); 121.5 (C-9); 123.9 (C-3); 127.9 (C-8); 131.0 (C-6); 140.2 (C-10); 164.5 (C-2); 167.9 ($\underline{C}O_2Et$). Found, *m/z*: 271.1442 $[M+H]^+$. $C_{16}H_{19}N_2O_2$. Calculated, *m/z*: 271.1441.

2-*tert*-Butyl-5-iodoimidazo[1,2-*a*]pyridine (6). Freshly distilled THF (150 ml), TMEDA (0.36 ml, 4.0 mmol), and 2-*tert*-butylimidazo[1,2-*a*]pyridine (**3**) (500 mg, 2.9 mmol) were inserted into a 250-ml round-bottom 3-neck flask with an addition funnel installed. The solution was degassed, filled with argon, and cooled to –80°C. Then BuLi (4 mmol, 1.8 ml of 2.24 M hexane solution) was added dropwise. The temperature of the mixture gradually grew

to –10°C and was kept at that point during 2 h. Then the flask was cooled back to –80°C and iodine (1.02 g, 4 mmol) together with anhydrous THF (~10 ml) were added in one portion. The mixture gradually heated up to room temperature. Then the dark-brown mixture was quenched with saturated solution of NH_4Cl and extracted with EtOAc. Organic extracts were combined and washed with a solution of Na_2SO_3 (until the complete discoloration) and then with brine. The solution was then dried over Na_2SO_4 and concentrated under the low pressure. Yield 0.870 g (96%), brown crystals, mp 60°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (9H, s, $C(CH_3)_3$); 6.90 (1H, dd, *J* = 8.8, *J* = 7.2, H-7); 7.24 (1H, d, *J* = 7.2, H-8); 7.52 (1H, s, H-3); 7.62 (1H, d, *J* = 8.8, H-6). ^{13}C NMR spectrum, δ, ppm: 30.2 $C(\underline{C}H_3)_3$); 32.4 ($\underline{C}(CH_3)_3$); 84.6 (C-5); 112.1 (C-3); 116.7 (C-8); 123.9 (C-6); 124.7 (C-7); 144.3. Found, *m*/*z*: 301.0193 $[M+H]^+$. $C_{11}H_{14}IN_2$. Calculated, *m*/*z*: 301.0196.

Ethyl 3-(2-*tert*-butylindolizin-5-yl)propiolate (7) was synthesized from 2-*tert*-butyl-5-iodoindolizine (**5**) according to procedure described earlier.[5] Yield 0.135 g (50%), red oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33–1.38 (12H, m, CH_3, $C(CH_3)_3$); 4.33–4.39 (2H, m, CH_2); 6.52 (1H, s, H-1); 6.58 (1H, dd, *J* = 9.0, *J* = 7.0, H-7); 6.96 (1H, d, *J* = 7.0, H-8); 7.41 (1H, d, *J* = 9.0, H-6); 7.55 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.1 (CH_3); 30.1 ($C(\underline{C}H_3)_3$); 31.8 ($\underline{C}(CH_3)_3$); 62.4 (CH_2); 88.2 (C≡C); 88.8 (C≡C); 99.9 (C-1); 110.0 (C-3); 115.2 (C-7); 120.1 (C-8); 121.9 (C-6); 128.2 (C-5); 132.5 (C-9); 139.7 (C-2); 153.3 (COOEt). Found, *m*/*z*: 270.1488 $[M+H]^+$. $C_{17}H_{20}NO_2$. Calculated, *m*/*z*: 270.1489. Found, %: C 75.94; H 6.86; N 5.13. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20.

Synthesis of compounds 8a–c *via* the Sonogashira reaction of 2-*tert*-butyl-5-iodoimidazo[1,2-*a*]pyridine (6) (General method). To a solution of 2-*tert*-butylimidazo[1,2-*a*]-pyridine (**3**) (1.1 equiv) in anhydrous MeCN (100 ml), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CuI (0.05 equiv), and the terminal alkyne (1 equiv) were added under an inert atmosphere (argon). Then Et_3N (0.1 equiv) was added to the mixture while stirring at room temperature. Gradually the mixture became a yellowish solution with slight fluorescence. The mixture was stirred for 45 min, and then the solvent was evaporated under reduced pressure; the concentrated mixture was separated by column chromatography (hexane–EtOAc, 10:1).

Ethyl 3-(2-*tert*-butylimidazo[1,2-*a*]pyridin-5-yl)-propiolate (8a) was synthesized from imidazo[1,2-*a*]-pyridine **6** and methyl prop-2-ynoate. Yield 0.122 g (45%), brownish-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (12H, s, CH_3, $C(CH_3)_3$); 4.29–4.33 (2H, m, CH_2); 7.06 (1H, dd, *J* = 8.8, *J* = 5.4, H-7); 7.14 (1H, d, *J* = 5.4, H-8); 7.61 (1H, s, H-3); 7.67 (1H, d, *J* = 8.8, H-6). ^{13}C NMR spectrum, δ, ppm: 13.9 (CH_3); 30.1 ($C(\underline{C}H_3)_3$); 32.4 ($\underline{C}(CH_3)_3$); 62.5 (CH_2); 88.1 (C≡C); 107.4 (C≡C); 120.1 (C-3); 120.2 (C-8); 122.5 (C-6); 123.6 (C-7); 124.3 (C-5); 144.1 (C-2); 153.0 (C-9); 158.3 ($\underline{C}O_2Et$). Found, *m*/*z*: 271.1443 $[M+H]^+$. $C_{16}H_{19}N_2O_2$. Calculated, *m*/*z*: 271.1441.

2-*tert*-Butyl-5-(phenylethynyl)imidazo[1,2-*a*]pyridine (8b) was synthesized from imidazo[1,2-*a*]pyridine **6** and phenylacetylene. Yield 0.214 g (78%), yellow crystals, mp 67°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (9H, s, $C(CH_3)_3$); 6.89 (1H, d, *J* = 7.5, H-8); 7.09 (1H, dd, *J* = 8.6, *J* = 7.7, H-7); 7.54 (1H, s, H-3); 7.61–7.68 (6H, m, H-6, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.2 ($C(\underline{C}H_3)_3$); 32.4 ($\underline{C}(CH_3)_3$); 82.1; 85.7; 102.0 (C-3); 116.9 (C-8); 117.1 (C-6); 123.6; 125.8 (C-7); 128.4; 128.9; 132.0; 144.2; 152.2; 157.3. Found, *m*/*z*: 275.1510 $[M+H]^+$. $C_{19}H_{19}N_2$. Calculated, *m*/*z*: 275.1543.

4-[(2-*tert*-Butylimidazo[1,2-*a*]pyridin-5-yl)ethynyl]-benzonitrile (8c) was synthesized from imidazo[1,2-*a*]-pyridine **6** and 4-ethynylbenzonitrile. Yield 0.224 g (75%), yellow crystals, mp 88°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (9H, s, $C(CH_3)_3$); 7.10 (1H, d, *J* = 7.8, H-8); 7.17 (1H, dd, *J* = 8.8, *J* = 7.5, H-7); 7.64 (1H, s, H-3); 7.69–7.75 (5H, m, H-6, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.2 ($C(\underline{C}H_3)_3$); 32.4 ($\underline{C}(CH_3)_3$); 85.1 (C≡C); 95.7 (C≡C); 107.1 (C-3); 113.1 (C-4'); 117.9 (CN); 118.1 (C-8); 118.2 (C-6); 119.2 (C-1'); 123.7 (C-3'); 126.2 (C-7); 132.3 (C-2'); 144.2 (C-5); 157.2 (C-2); 157.3 (C-9). Found, *m*/*z*: 300.1497 $[M+H]^+$. $C_{20}H_{18}NO_3$. Calculated, *m*/*z*: 300.1495.

Ethyl 3-*tert*-butyl-1-(3-ethoxy-3-oxoprop-1-yn-1-yl)-pyrrolo[2,1,5-*cd*]indolizine-2-carboxylate (9). The procedure[5] was the same used to synthesize compound **7**, but instead of using equimolar amount of alkyne (ethyl prop-2-ynoate) an excess of it (>3 equiv) was introduced into the reaction. The amounts of reagents were as follows: 0.299 g (1.0 mmol) of 2-*tert*-butyl-5-iodoindolizine (**5**), 0.300 g (3.06 mmol, 3.06 equiv) of ethyl prop-2-ynoate, 0.035 g of $Pd(PPh_3)_2Cl_2$ (0.05 mmol, 0.05 equiv), and 0.010 g of CuI (0.05 mmol, 0.05 equiv) in dry MeCN (100 ml). The product was purified by column chromatography (hexane–EtOAc, 3:1). Yield 0.204 g (56%), dark-red crystals, mp 96°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25–1.34 (15H, m, $2CH_3$, $C(CH_3)_3$); 4.30 (2H, q, *J* = 6.9, CH_2); 4.57 (2H, q, *J* = 6.9, CH_2); 7.15 (1H, s, H-1); 7.76 (1H, dd, *J* = 7.9, *J* = 7.3, H-8); 7.84 (1H, d, *J* = 7.3, H-9); 8.19 (1H, d, *J* = 7.8, H-7). ^{13}C NMR spectrum, δ, ppm: 14.2 (CH_3); 14.3 (CH_3); 29.6 ($C(\underline{C}H_3)_3$); 31.2 ($\underline{C}(CH_3)_3$); 60.2 (OCH_2); 61.7 (OCH_2); 104.4; 110.1; 114.2; 117.5; 118.8; 122.1; 123.3; 127.3; 131.4; 137.9; 149.5; 157.0; 165.9 ($\underline{C}O_2Et$); 166.2 ($\underline{C}O_2Et$).

X-ray structural analysis of compounds 2, 6, 9 was performed on a single crystal diffractometer CAD-4 (Enraf-Nonius, the Netherlands), Cu*K*α beam with graphite monochromator, as well as on a single crystal diffractometer STADIVARI Pilatus 100K (Stoe & Cie, Germany), Cu*K*α beam with focusing mirrors. Compounds **2**, **6** were recrystallized from $CHCl_3$, compound **9** – from hexane–ethylacetate, 5:1. The structures were solved with the direct method using the SHELXS-97[8a] program set and refined by the full-matrix least-squares technique using the SHELXL-2013[8b] program set in anisotropic approximation for all non-hydrogen atoms. Hydrogen atom positions were found from difference electron density synthesis and were refined according to the "rider" model. Absorption corrections were calculated with DIFABS[8c] by determining equivalent reflections. The full set of X-ray structural data for compounds was deposited at the Cambridge Crystallographic

Data Center (deposits CCDC 1828872 (compound **2**), CCDC 1828871 (compound **6**), CCDC 1828873 (compound **9**)).

The Supplementary information file containing the full set of X-ray structural analysis data for structures **2**, **6**, **9** is available at the journal website at http://hgs.osi.lv.

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