JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Pyrrolotriazoloisoquinoline Frameworks by Intramolecular Cu-Mediated or Free Radical Arylation of Triazoles

Liya D. Funt, Olesya A. Tomashenko, Ivan P. Mosiagin, Mikhail S. Novikov, and Alexander F. Khlebnikov*

Institute of Chemistry, Saint Petersburg State University, 7/9 Universitetskaya nab., St. Petersburg 199034, Russia

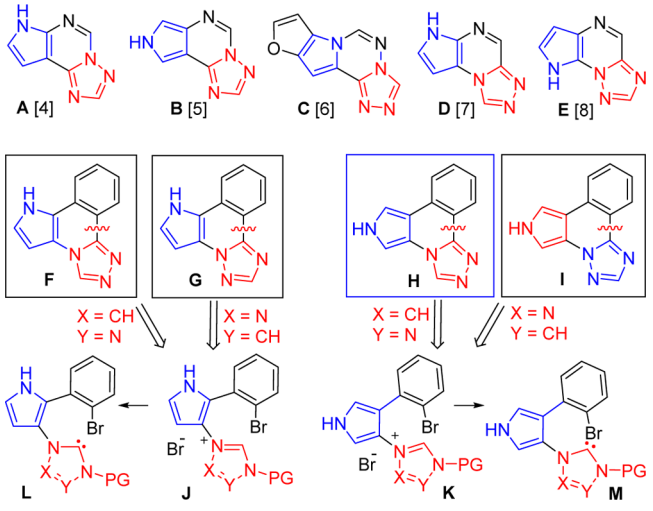
Supporting Information

ABSTRACT: The cyclization of (2-bromophenyl)pyrrolyl-1,2,4-triazoles via copper-mediated intramolecular direct C-arylation of 1,2,4-triazoles was first accomplished under triazole-NHC control to give unknown fused heterocyclic skeletons, pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*] or [3,4-*a*]-isoquinolines. The primary products underwent a triazole ring opening under the basic arylation conditions, providing *N*-(1*H*-pyrrolo[3,2-*c*]isoquinolin-5-yl)cyanamides. The formation of the cyanamides from isomeric pyrrolo[3,2-*c*][1,2,4]-triazolo[3,4-*a*]isoquinolines involves, besides the triazole ring opening, the unusual migration of the cyano group. Cyanamides can be easily reduced to 1*H*-pyrrolo[3,2-*c*]isoquinolin-5-amines, the first NH_2-substituted derivatives of 1*H*-pyrrolo[3,2-*c*]isoquinoline. An insight into the mechanism of the triazole ring cleavage was achieved by performing a DFT study at the B3LYP/6-31G+(d,p) level. Free radical cyclization of (2-bromophenyl)pyrrolyl-1,2,4-triazoles with TTMSS/AIBN under neutral conditions allows obtaining pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*] and [3,4-*a*]isoquinolines, as well two more new heterocyclic systems, pyrrolo[3,4-*c*][1,2,4]triazolo[5,1-*a*] and [3,4-*a*]isoquinolines, in good yields without triazole ring cleavage. The developed cyclizations provide a concise, atom-economical route to novel fluorescent fused polyheterocycles containing pyrrole and 1,2,4-triazole moieties.

INTRODUCTION

Nitrogen-containing *ortho*-fused polyheteroaromatic compounds, containing a pyrrole core, have a significant importance in the development of new perspective materials in particular for bioimaging applications and chemosensor systems.[1] At the same time, compounds containing 1,2,4-triazole ring demonstrate wide range of biological activity[2] and also are extensively used in material science.[3] Meanwhile, the number of tri- and tetracyclic aromatic skeletons with series-connected pyrrole, azine, and 1,2,4-triazole rings is sorely limited. Thus, only derivatives of 7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **A**,[4] 8*H*-pyrrolo[3,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **B**,[5] furo-[2′,3′:4,5]-pyrrolo[1,2-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazine **C**,[6] 6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo-[4,3-*a*]pyrazine **D**,[7] and 8*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*a*]pyrazine **E**[8] were previously synthesized (Scheme 1). Approaches to the formation of polycycles **A**–**E**, with a diazine or triazine as the central ring, are based on condensation reactions. In this work, we set out to develop a general approach to a series of new *ortho*-fused heterocycles **F**–**I** (Scheme 1) with isoquinoline core as a link between the pyrrole and 1,2,4-triazole rings. We suggested that the recently developed synthesis of pyrrolyl-1,2,4-triazolium salts,[9] based on the general strategy for the synthesis of 3-heterylpyrroles,[10] could be a benchmark for solving this task if we start from (2-bromophenyl)-substituted analogues **J**, **K** (Scheme 1).

Scheme 1. Known (A–E) and Novel (F–I) Fused Polyheterocycles Containing Pyrrole and 1,2,4-Triazole Moieties



Two approaches for the transformation of compounds **J** and **K** into products **F**, **G** and **H**, **I**, respectively, could potentially be

Received: May 31, 2017
Published: June 30, 2017

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583–7594

applied. Recently we demonstrated that NHC (N-heterocyclic carbene) can serve as the guiding factor in a copper-catalyzed intramolecular C-arylation of pyrrolylimidazolium salts.[11] It was also found that pyrrolyltriazolium salts of **J**, **K** type react with bases under mild conditions to form the corresponding triazole NHCs **L**, **M** (Scheme 1).[9] Therefore, we hypothesized that triazole-NHCs **L**, **M** may participate in the formation of Cu-complexes with Cu(I) followed by the selective intramolecular C-arylation of the triazole ring by the *ortho*-brominated phenyl substituent at the pyrrole ring. This would demonstrate a new approach to a solution of the selectivity problem of the direct C−H arylation of triazoles, using generation of triazole NHC under arylation conditions, and would provide easy access to the unknown heterocycle frameworks. An obstacle in using the Cu-catalyzed arylation, which has worked well in the case of imidazoles, in the case of triazoles may be low stability of triazolium salts in the basic medium. The second approach, free radical arylation of the triazole ring in **J**, **K**, could be the valuable alternative for copper-catalyzed reactions, since it can be performed in neutral medium, although examples of such reactions have not been published up to now. Herein, our detailed studies on assembling of **F**−**I** skeletons using Cu-mediated and free radical intramolecular arylation of 1,2,4-triazoles are described.

RESULTS AND DISCUSSION

Two sets of 2-bromophenyl-substituted 4*H*-pyrrolyl-4*H*-1,2,4- and 1*H*-pyrrolyl-1*H*-1,2,4-triazolium salts **3** and **4** were synthesized in good to moderate yields (Scheme 2) from *N*-phenacyltriazolium bromides **1** and 2*H*-azirines **2** by the published procedure.[9]

Salts **3** were introduced into Cu-mediated intramolecular direct arylation (Table 1). It was found that the highest yields of arylation products could be obtained at an unusually low for

Scheme 2. Synthesis of Pyrrolyltriazolium Salts 3, 4

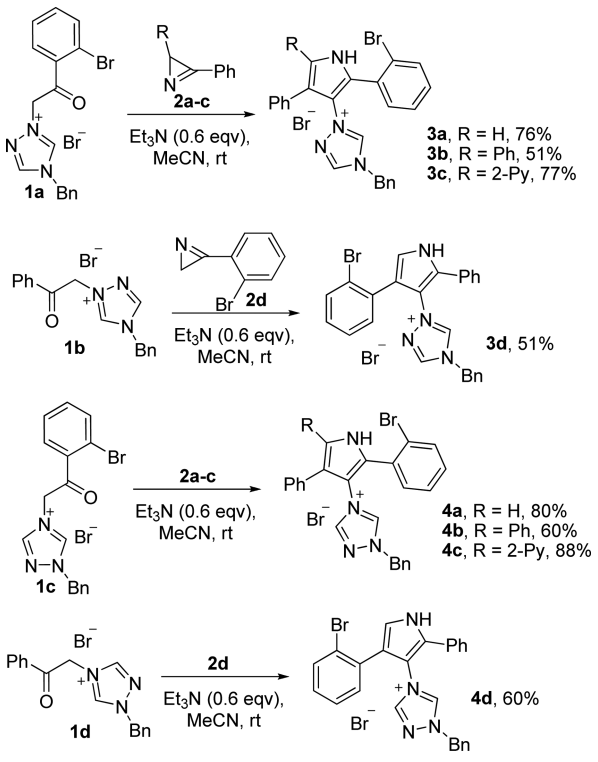
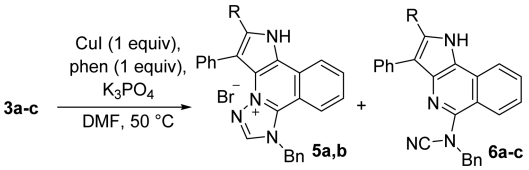


Table 1. Cu-Mediated Cyclization of Salts 3a−c



entry	R	3	K_3PO_4 (equiv)	time (d)	5, yield (%)	6, yield (%)
1	H	**a**	0.8	1	**a**, 15[a]	**a**, 67[a]
2	H	**a**	1.05	1	**a**, 13[b]	**a**, 81[b]
3	H	**a**	2	1		**a**, 98
4	Ph	**b**	2	2	**b**, 42	**b**, 51
5	Ph	**b**	2	4	**b**, 8	**b**, 83
6	2-Py	**c**	2	5		**c**, 63

[a]Along with starting material **3a** (13%). [b]Along with starting material **3a** (3%).

the copper-catalyzed arylation of 1,2,4-triazoles temperature of 50 °C. Typically heating to 120−150 °C is required.[12] Use of 1 equiv of CuI, 1 equiv of phenanthroline as a ligand, and 0.8 equiv of K_3PO_4 as a base leads to the isolation of target bromide **5a** (15%), cyanamide **6a** (67%), and starting material **3a** (13%) (Table 1, entry 1). Growth of amount of K_3PO_4 (1.05 equiv) increased conversion of the starting material, but led to decreasing the yield of bromide **5a** and increase the yield of cyanamide **6a** (Table 1, entry 2). And at last, use of 2 equiv of K_3PO_4 afforded cyanamide **6a** in 98% yield as the only product (Table 1, entry 3). Compound **6a** could be formed via the triazole ring opening in the primary arylation product **5a**. Cleavage of the triazole ring with the formation of cyanamide derivatives was earlier observed under the action of a base on fused 1,2,4-triazolium salts, 1*H*-[1,2,4]triazolo[1,5-*c*]pyrimidin-4-ium iodides,[13a] and 3*H*-[1,2,4]triazolo[1,5-*a*]pyrimidinium bromides.[13b] Triazol-1-ium bromide **3b** gave two products under the same conditions, the expected product of arylation **5b** and the product of triazole ring opening, cyanamide **6b**, the ratio of the products being dependent on the reaction time (Table 1, entries 4, 5). In the case of **3c** only cyanamide **6c** was isolated. The reaction of 4*H*-1,2,4-triazol-1-ium bromide **3d** gave complex mixture of unidentified products.

All new compounds were characterized by ^1H and ^{13}C NMR, IR spectroscopy, and mass spectrometry. The structure of **6a** was confirmed by XRD-analysis (Figure 1).

The following scheme of the formation of **5** and **6** can be proposed (Scheme 3).

Pyrrolyltriazolium salt **3** loses HBr under basic conditions (K_3PO_4) and affords betaine **7**, which is in tautomeric equilibrium with carbene **8**. The latter forms a complex **9** with Cu(I),[14] which cyclization leads to the formation of product **5**. Salt **5** produces cyanamide **6**, probably via dehydrobromination into **10** and formation of anion **11** under the basic conditions, followed by the triazole ring opening to anion **12** and its protonation. In order to make sure that the cyclization occurs before the triazole ring opening, isolated compound **5b** was heated in DMF with and without K_3PO_4. Salt **5b** was quantitatively transformed into **6b** in the presence of K_3PO_4 in 24 h at 50 °C, whereas in the absence of the base no reaction was observed. Conversion of the starting pyrrolyltriazolium salt **3** requires up to 5 days (monitored by ^1H NMR). During this time a part of the cyclization product **5** turns into cyanamide **6** through the triazole ring opening under the reaction conditions. For example, the ratio of **5b**:**6b** after 2

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

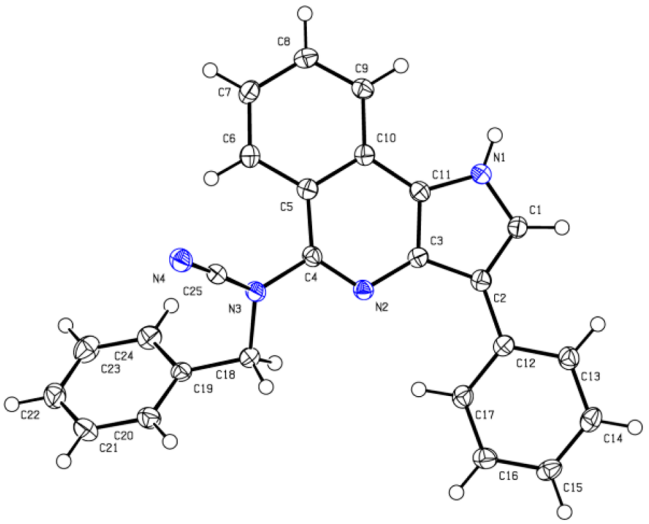
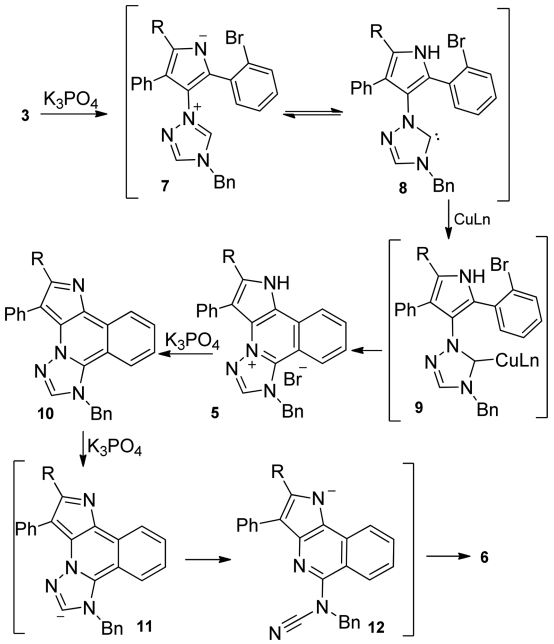


Figure 1. Molecular structure of compound **6a**, 50% thermal ellipsoids are shown.

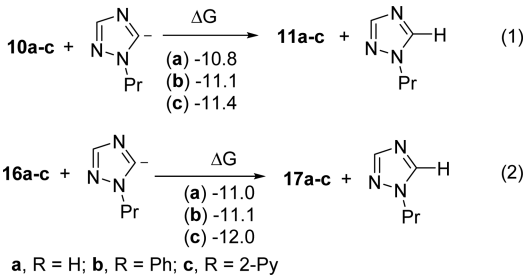
Scheme 3. Proposed Mechanism of Transformations of Salts 3a–c under the Cu-Mediated Conditions



days was 1:1.2 whereas after 4 days it was already 1:10 (Table 1, entries 4, 5). To shed some light on the mechanism of the formation of cyanamides **6** the quantum chemical calculations of the compounds under consideration were performed. First of all, the calculated Gibbs free energies of compounds **10a–c** and anions **11a–c** were used to evaluate the possibility of the deprotonation of **10a–c** by K_3PO_4 from the isodesmic eq (Scheme 4, eq 1). According to the eq (1), the acidity of **10a–c** in DMF should be higher than the acidity of 1-propyl-1*H*-1,2,4-triazole (pK_a 26.2, THF[15]), which could be deprotonated by K_3PO_4 in DMF.[16]

The calculated barriers for transformation of intermediates **11a–c** to nitriles **12a–c** slightly depend on the substituent and are only 7.9–8.1 kcal/mol (Figure 2). Therefore, the rate of this transformation depends only on the rate of deprotonation of **10a–c** under the reaction conditions.

Scheme 4. Isodesmic Equations (1, 2) for the Proton Transfer in Compounds 10a–c, 16a–c and *N*-Propyl-1,2,4-triazole[a]



[a] ΔG, kcal/mol, 298 K, DMF, B3LYP/6-31G+(d,p).

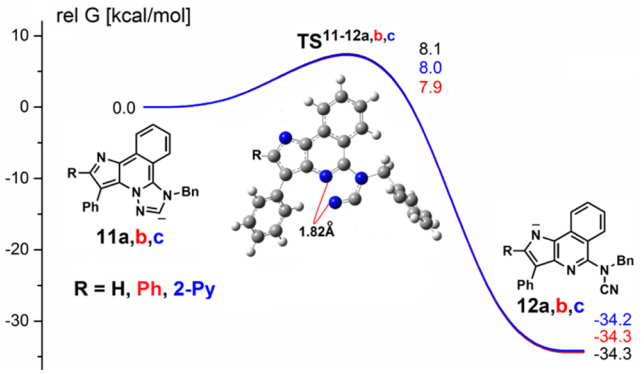
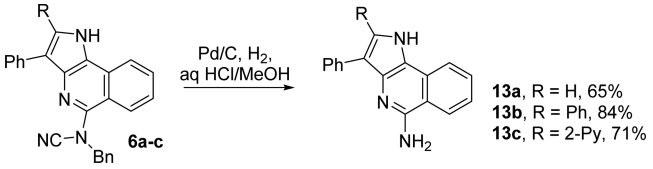


Figure 2. Relative Gibbs free energies (in kcal/mol, 298 K, PCM model for DMF) of molecules **11**, **12a–c** and the transition state **11→12** computed at the B3LYP/6-31G+(d,p) level.

The results described above indicate that a two-step sequence involving the transformation of the phenacyl substituent in *N*-phenacyltriazolium salts into diarylpyrrolyl moiety by the reaction with arylazirines followed by Cu(I)-mediated intramolecular C-arylation can be a good two-step method for the preparation of cyanamides **6**. The latter compounds can be easily reduced to 1*H*-pyrrolo[3,2-*c*]-isoquinolin-5-amines **13**, the first NH_2-substituted derivatives of 1*H*-pyrrolo[3,2-*c*]isoquinoline, with average to high yields (Scheme 5). Note that the possibility of application for the

Scheme 5. Synthesis of 1*H*-Pyrrolo[3,2-*c*]isoquinolin-5-amines 13 from Cyanamides 6



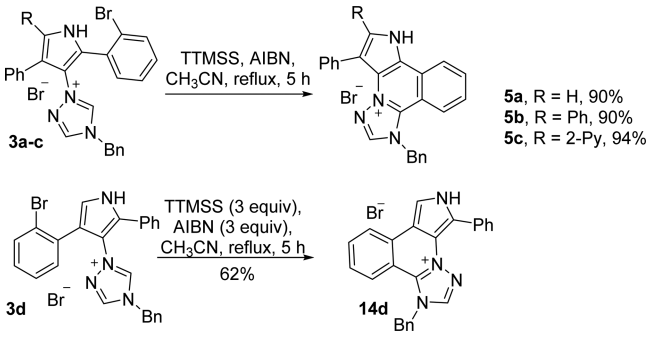
treatment of cognitive disorders associated with Alzheimer's disease has been shown recently for some 4-(pyrrolidine-3-yl-amino)-1*H*-pyrrolo[3,2-*c*]quinoline.[17]

Although unexpected rearrangement of pyrrolo[3,2-*c*]-[1,2,4]triazolo[5,1-*a*]isoquinolines **10** leads to valuable 1*H*-pyrrolo[3,2-*c*]isoquinolin-5-amines **13** we nevertheless searched for another approach which would allow to accomplish desired intramolecular C-arylation without any subsequent transformations to obtain compounds **5**, possessing a novel heterocyclic skeleton, as the main product. In our case it

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583–7594

meant that basic conditions would have to be excluded. Despite the lack of information on radical intra- or intermolecular arylation of triazoles we tried to accomplish radical cyclization with tris(trimethylsilyl)silane/azobis(isobutyronitrile) (TTMSS/AIBN) system. To our pleasure pyrrolyltriazolium salts **5** with skeleton **G** (Scheme 1) were obtained in high yields under these conditions (Scheme 6). Moreover, salt **3d** which

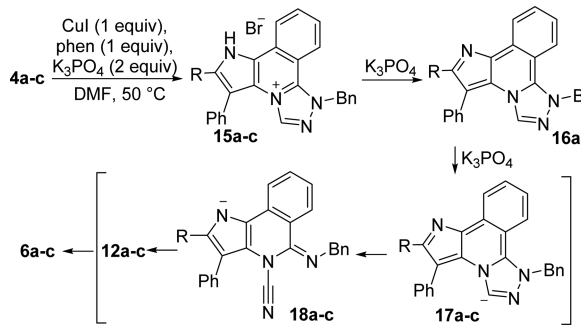
Scheme 6. Radical Cyclization of Salts 3a–d into Salts 5a–c and 14d



failed to cyclize under Cu(I)-catalysis afforded under radical reaction conditions the corresponding salt **14d**, the derivative of a new heterocyclic system, pyrrolo[3,4-*c*][1,2,4]triazolo[5,1-*a*]isoquinoline (skeleton **I**, Scheme 1), in 62% yield.

We expected that the cyclization of the 1-benzyl-4-(2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromides **4a–c** under Cu(I)-catalysis would lead to the single product **15** (Table 2) since the triazole ring opening via the

Table 2. Cyclization of Salts 4a–c



entry	R	4	time (d)	**15**, yield (%)	**6**, yield (%)
1	H	**a**	4	**a**, 50	**a**, 48
2	Ph	**b**	4	**b**, 84	**b**, 14
3	2-Py	**c**	6	**c**, 10	**c**, 34

above-mentioned route in this case is impossible without the loss of aromaticity. To our surprise for all three 1*H*-1,2,4-triazol-4-ium bromides **4a–c** we obtained the expected products of intramolecular arylations **15a–c**, possessing a novel heterocyclic skeleton F (Scheme 1), along with the abnormal products of triazole ring opening, which were identical to compounds **6a–c** (Table 2). The formation of the latter should apparently involve the migration of the cyano group to keep the aromaticity of the system. The 1*H*-1,2,4-triazol-4-ium bromide **4d** did not give the target cyclization product under Cu-catalyzed reaction conditions (complex mixture of unidentified products formed).

The acidity in DMF of **16a–c**, according to the isodesmic eq (Scheme 4, eq 2), should be higher than the acidity of 1-propyl-1*H*-1,2,4-triazole and, therefore, they could be deprotonated by K_3PO_4 in DMF.[16] According to DFT calculations (Figure 3),

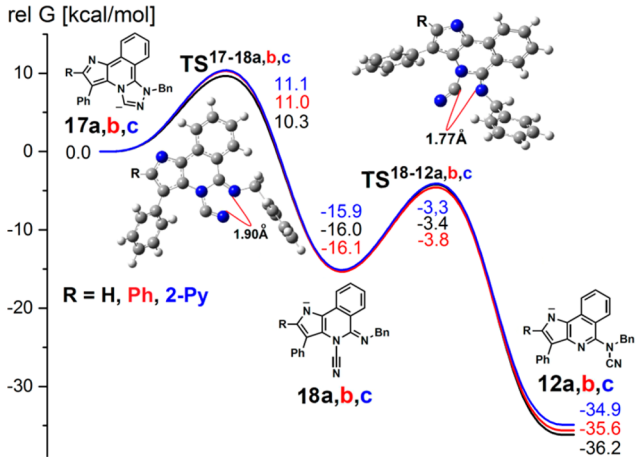
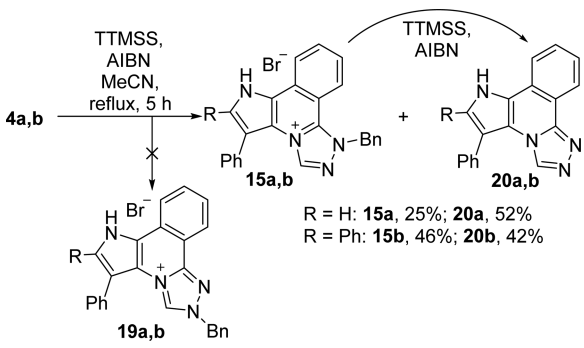


Figure 3. Relative Gibbs free energies (in kcal/mol, 298 K, PCM model for DMF) of molecules **12**, **17**, and **18a–c** and the transition states **17→18a–c** and **18→12a–c** computed at the B3LYP/6-31G+(d,p) level.

the barrier for the transformation of anions **17a–c** to cyano-substituted anions **18a–c** is only 10–11 kcal/mol. Intermediates **18a–c** can rearrange to aromatic anions **12a–c** by migration of the cyano group through the pseudopericyclic transition states $\mathbf{TS}^{18-12}$ with Gibbs free energies much lower than those for $\mathbf{TS}^{17-18}$. The driving force for the rearrangement of compounds **16a–c** upon heating under basic conditions is therefore their lower thermodynamic stability compared to the stability of the compounds **6a–c.**

To suppress the triazole ring cleavage in **15** we tried again the radical cyclization of bromides **4** under neutral conditions. Free radical cyclization of pyrrolyltriazolium bromides **4** in theory may lead to two products **15** and **19** since there are two nonequivalent positions in the triazolium ring for attack by the radical species (Scheme 7). Salts **4a,b** were introduced into

Scheme 7. Radical Cyclization of 4a,b

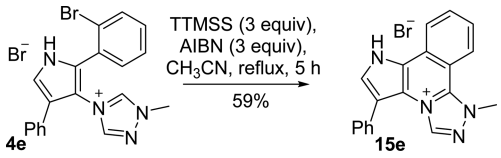


radical cyclization but instead of two saline isomers **15a,b** and **19a,b** only pyrrolyltriazolium salts **15a,b** were obtained along with debenzylated isoquinolines **20a,b** (Scheme 7). Salt **15b** can be partly reduced to **20b** under action of TTMSS (2 equiv)/AIBN (2 equiv) in refluxing acetonitrile with conversion 13% for 5h.

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583–7594

Salts **19a,b** were not detected in the reaction mixtures even if low concentration of TTMSS was maintained through slow addition of reagents. One of the explanations for the lack of isomers **19** among the reaction products could be their fast conversion to compounds **20** by debenzylation under the reaction conditions. To exclude this possibility the methyl derivative **4e** was synthesized, for which such transformation is impossible, and introduced into radical cyclization (Scheme 8).

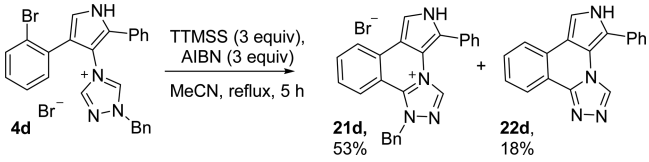
Scheme 8. Radical Cyclization of Methyl Substituted Salt 4e



Methyl group cannot be eliminated by TTMSS so if two isomers had been formed we would have detected both of them but the only product of the reaction was the isomer **15e**. The structure of **15e** was additionally confirmed by NOESY and HMBC spectra (see SI).

The 1*H*-1,2,4-triazol-4-ium bromide **4d**, which cannot be cyclized under Cu-catalysis, gave salt **21d** and its debenzylation product (**22d**), both possessing the backbone **H**, under the radical reaction conditions (Scheme 9).

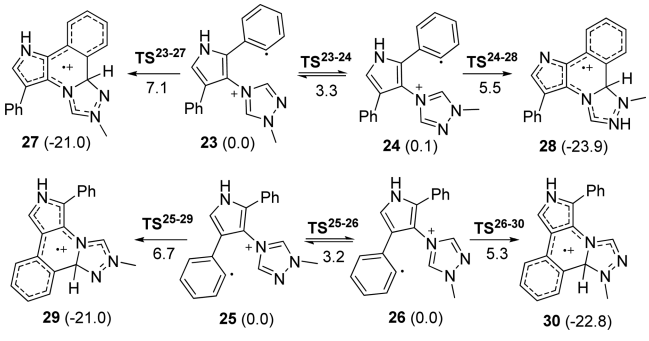
Scheme 9. Radical Cyclization of Salt 4d



To reveal the possible cause of regioselectivity of the radical cyclization in the case of 1*H*-1,2,4-triazol-4-ium bromides **4** the computations of relative Gibbs free energies for the cyclization of the corresponding model radical-cations **23**−**26** were performed (Scheme 10).

The data obtained show that regioselectivity of radical cyclizations of **4a,b,e**, and **4d** is probably due to the lower barriers for the cyclization of radical-cation **24** and **26** (leading to the formations analogues of **4a,b,e** and **4d**), than barriers for the cyclization of radical-cation **23** and **25**, leading to the formation of the corresponding regioisomers. The found

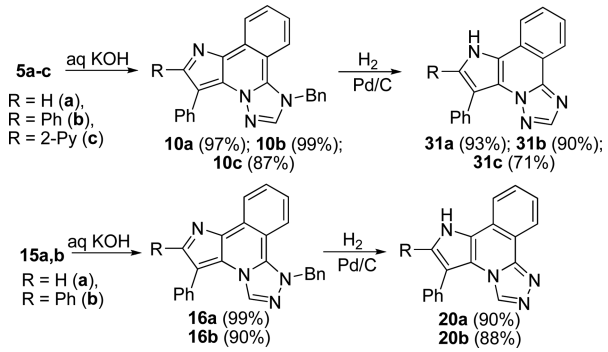
Scheme 10. Relative Gibbs Free Energies (in kcal/mol, 298 K, PCM model for MeCN) for the Cyclizations of Radical-Cations 23−26 Computed at the B3LYP/6-31G+(d,p) Level



energy differences for the model compounds should lead to selectivity better than 10:1.

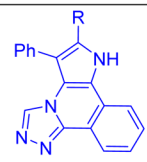
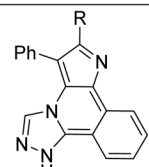
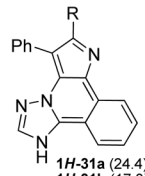
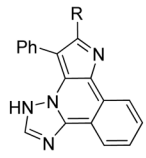
The pyrrolotriazoloisoquinolin-4-ium bromides **5** and **15** can be quantitatively dehydrobrominated without the triazole ring-opening by a heterogeneous reaction with aq KOH at rt, and then debenzylated cleanly into compounds **31a−c** in good yields (Scheme 11).

Scheme 11. Dehydrobromination of Salts 5a−c and 15a,b and Debenzylation of Compounds 16a,b and 10a−c



Compounds **31a−c** and **20a,b** prepared by the reductive debenzylation of **10a−c** and **16a,b** in contrast to isoquinolines **10** and **16** can exist in several tautomeric forms. According to DFT calculations at the B3LYP/6-31G+(d,p) level with the PCM model for DMSO at 298 K, the tautomer with a 1*H*-pyrrol moiety (7*H*-**31a,b** and 7*H*-**20a,b**) for all heterocyclic skeletons is much more stable than others (Table 3). This is in

Table 3. Relative Gibbs Free Energies for Tautomers 20a,b and 31a,b[a]

31,**20**	Tautomers (relative Gibbs free energies, kcal/mol)		
20a,b			**1*H*-20a** (16.0) **1*H*-20b** (15.1)
	7*H*-**20a,b** (0)	1*H*-**20a,b**	
31a,b			
	7*H*-**31a,b** (0)	**1*H*-31a** (24.4) **1*H*-31b** (17.8)	**3*H*-31a** (18.4) **3*H*-31b** (23.3)

[a] ΔG, kcal/mol B3LYP/6-31G+(d,p), PCM model for DMSO at 298 K.

agreement with NMR spectra of **20a** in DMSO-d_6 (H^1, HSQC $^1H-^{15}N$, and HMBC $^1H-^{15}N$ spectra, see SI). The existence of compounds **10**, **16** and **31**, **20**, respectively, in the different tautomeric forms, can lead to substantial distinctions in their photophysical properties (*vide infra*).

Prepared by the intramolecular arylation from pyrrolyltriazoles **3**, **4** novel fused heterocyclic systems **5**, **15** as well as their dehydrobrominated (**10**, **16**), debenzylated derivatives (**31**, **20**)

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

Table 4. Photophysical Characteristics of Selected Pyrrolotriazoloisoquinolines 10b and 16a,b; Their Derivatives 5b, 15b, 31b, and 20a,b; and Substituted Pyrroloisoquinolines 6a−c and 13a−c in Methanol Solutions at Room Temperature

entry	compound	absorbance, λ_{max}, nm (ε, $10^{-3}\cdot M^{-1}\cdot cm^{-1}$)	emission, λ_{max}, nm (QY, %)	excitation, λ_{max}, nm
1	**5b**	245(37); 317(35); 424(10)	544	316, 390, 430(sh)
2	**6a**	252(49); 286(46); 328(16)	480 (3)	287, 331, 354(sh)
3	**6b**	246(73); 257(68); 291(95); 373(28)	460 (9)	288, 369
4	**6c**	283(35); 336(19); 367(19); 381(18)	437 (13)	285, 337, 365, 380
5	**10b**	247(24); 317(23); 424(6)	546	318, 389, 429(sh)
6	**13a**	260(26); 286(26); 364(8)	438 (28)	262, 288, 363
7	**13b**	290(35); 339(18); 372(15)	438 (32)	290, 339, 370(sh)
8	**13c**	287(31); 375(25); 388(23)	436 (13)	287, 373, 387
9	**15b**	257(25); 321(23); 441(8)	559	320, 442
10	**16a**	257(65.5); 369(12)	468	256, 370
11	**16b**	257(29), 321(27); 442(9.5)	559	320, 440
12	**20a**	248(44); 255(43.5); 293(14); 304(17); 329(4); 343(4)	385	254, 292, 344(sh)
13	**20b**	255(40); 323(32)	401	257, 323
14	**31b**	230(29.5); 271(26.5), 322(20)	400	273, 323

and products of triazole ring opening (**6**, **13**) are luminescent in solutions. The preliminary study of photophysical properties was performed for selected compounds. The corresponding data are listed in Table 4 and selected examples of absorption and emission spectra presented in Figures 4−6 (for the spectra of absorbance, emission, and excitation see Supporting Information, Figures S1−S14).

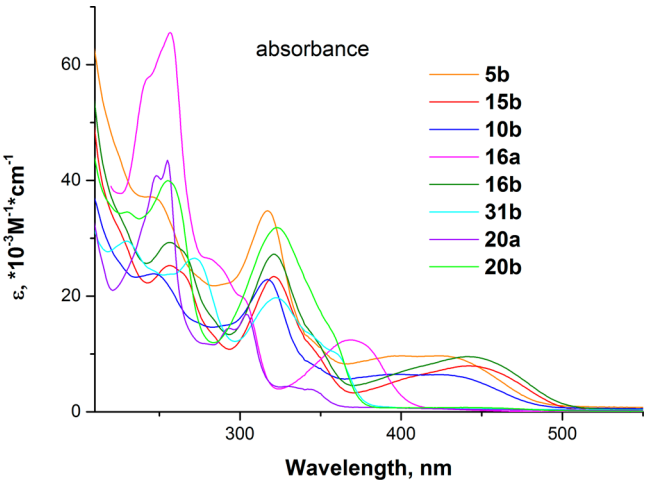


Figure 4. Absorption spectra of selected pyrrolotriazoloisoquinolines **10b**, **16a,b** and their derivatives **5b**, **15b** and **31b**, **20a,b** in methanol solutions at room temperature.

As was shown above, the benzyl group fixes isoquinolines **10** and **16** in the form of thermodynamically less stable tautomer, and its removal by hydrogenolysis leads to a more stable tautomer of the heterocycle. It significantly affects the absorption and the emission spectra (Table 4). Thus, the hypsochromic shift of the long-wave absorption band is **10b** (1*H*) → **31b** (7*H*) −102 nm (Table 4, entries 5, 14) and **16b** (1*H*) → **20b** (7*H*) −119 nm (Table 4, entries 11, 13), and the emission shift is **10b** (1*H*) → **31b** (7*H*) −146 nm and **16b** (1*H*) → **20b** (7*H*) −158 nm. Pyrrolotriazoloisoquinolinium bromides **5b**, **15b** and their dehydrobrominated derivatives pyrrolotriazoloisoquinolines **10b**, **16b** have almost identical spectra of absorbance and emission in methanol with emission maxima 546 nm for pair **5b**/**10b** and 559 nm for pair **15b**/**16b** (Table 4, Figures 4 and 5).

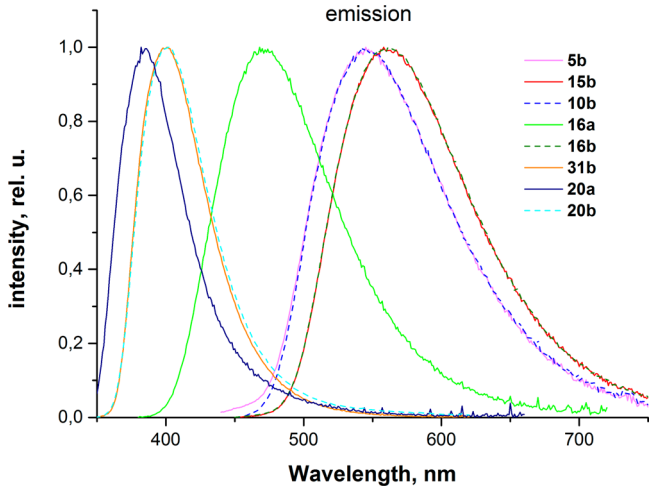


Figure 5. Emission spectra of selected pyrrolotriazoloisoquinolines **10b**, **16a,b** and their derivatives **5b**, **15b** and **31b**, **20a,b** in methanol solutions at room temperature.

Pyrroloisoquinolines **6** and **13** have similar spectra of absorbance (Table 4, Figure 6) and emission (Table 4) in methanol with emission maxima lying in the range of 436−480

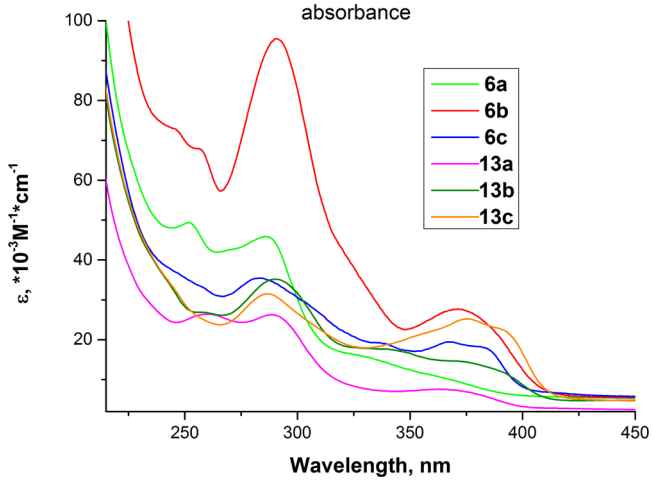


Figure 6. Absorption spectra of substituted pyrroloisoquinolines **6a−c** and **13a−c** in methanol solutions at room temperature.

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

nm. Quantum yields for cyanamides **6** and for 1*H*-pyrrolo[3,2-*c*]isoquinolin-5-amines **13** are up to 13 and 32%, respectively (Table 4).

CONCLUSIONS

In conclusion, pyrrolotriazoloisoquinolines, possessing four novel heterocyclic skeletons, were synthesized by the first copper-mediated intramolecular direct C-arylation of 1,2,4-triazoles under triazole NHC control and free radical cyclization. The copper-mediated cyclization of the starting (2-bromophenyl)pyrrolyltriazolium bromides proceeds via the formation of the corresponding NHCs under basic conditions of the arylation. The triazole NHCs can react with the Cu(I) to give the triazole NHC-Cu-complexes, which are the most probable reactive species providing selective arylation. The primary arylation products, 1-benzyl-1,7-dihydropyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*] and [3,4-*a*]isoquinolin-4-ium bromides, in the presence of a base and heating can undergo a triazole ring opening with formation of *N*-(1*H*-pyrrolo[3,2-*c*]-isoquinolin-5-yl)cyanamides, which can be efficiently reduced to 1*H*-pyrrolo[3,2-*c*]isoquinolin-5-amines, the first NH_2-substituted derivatives of 1*H*-pyrrolo[3,2-*c*]isoquinoline. The formation of the cyanamides from 1-benzyl-1,7-dihydropyrrolo-[3,2-*c*][1,2,4]triazolo[3,4-*a*]isoquinolin-4-ium bromides involves, besides the triazole ring opening, the migration of the cyano group to keep the aromaticity of the system. An insight into the mechanism of the triazole ring cleavage was achieved by performing a DFT study at the B3LYP/6-31G+(d,p) level. Free radical cyclization of (2-bromophenyl)pyrrolyl-1,2,4-triazoles with TTMSS/AIBN under neutral conditions allows obtaining pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*] and [3,4-*a*]-isoquinolines, as well two more new heterocyclic systems, pyrrolo[3,4-*c*][1,2,4]triazolo[5,1-*a*] and [3,4-*a*]isoquinolines, in good yields without triazole ring cleavage. The primary saline products can be dehydrobrominated in heterogeneous conditions at rt with preservation of the triazole ring to give derivatives of 1-benzyl-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*]-isoquinoline and 1-benzyl-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[3,4-*a*]isoquinoline, which are fixed in the thermodynamically unstable 1*H*-tautomeric forms. Debenzylation of these compounds leads via tautomerization to the more stable tautomers. The developed cyclizations provide a concise, atom-economical route to novel fluorescent heteropolycyclic systems, including compounds that could be used as fluorescent bidentate ligands.

EXPERIMENTAL SECTION

General Information and Methods. Melting points were determined on a melting point apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a NMR spectrometer in $CDCl_3$ and DMSO-d_6. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS δ = 0.00). ^{1}H NMR spectra were calibrated according to the residual peak of $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm). For all new compounds, ^{13}C {^{1}H} and ^{13}C DEPT-135 spectra were recorded and calibrated according to the peak of $CDCl_3$ (77.00 ppm) or DMSO-d_6 (39.51 ppm). Electrospray ionization (ESI) mass spectra were recorded on a mass spectrometer, HRMS-ESI-QTOF, electrospray ionization, positive mode. Single crystal X-ray data were collected by means of diffractometer at 100 K using monochromated Cu Kα radiation. Crystallographic data for the structure **6a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1509121). Compounds **1a−d**, **3a**, and **4a** were prepared by the reported procedures.[9]

*4-(2-(2-Bromophenyl)-2-oxoethyl)-1-methyl-1H-1,2,4-triazol-4-ium bromide (**1e**).* A solution of 2-bromo-1-(2-bromophenyl)ethan-1-one (1.006 g, 3.61 mmol) and 1-methyl-1*H*-1,2,4-triazole (300 mg, 3.61 mmol) in acetone (8 mL) was stirred under reflux for 18 h. Solid was filtered, washed with acetone (3 × 10 mL) and dried to obtain colorless product (275 mg, 21%), mp 80−81 °C. ^{1}H NMR (DMSO-d_6): δ 4.20 (s, 3H), 6.13 (s, 2H), 7.57−7.68 (m, 2H), 7.86 (dd, J = 7.8, 1.1 Hz, 1H), 8.07 (dd, J = 7.6, 1.7 Hz, 1H), 9.23 (s, 1H), 10.15 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 38.0 (CH_3), 55.1 (CH_2), 119.7 (C), 128.1 (CH), 131.0 (CH), 134.3 (CH), 134.6 (C), 134.8 (CH), 143.6 (CH), 145.4 (CH), 191.6 (C). HRMS (ESI) m/z: 282.0060 calcd for $C_{11}H_{11}BrN_3O^+$ [M−Br]$^+$, found 282.0071.

General Procedure (A) for the Synthesis of Pyrrolyltriazolium Bromides 3 and 4. Triethylamine (95 mg, 0.9 mmol, 0.6 equiv) was added dropwise to a stirred suspension of triazolium bromide **1a−e** (1.6 mmol) and 2*H*-azirine **2a−d** (2.3 mmol, 1.5 equiv) in acetonitrile (5 mL), and then the reaction mixture was stirred at rt for 24 h. The mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate. The precipitate was filtered, washed with ethyl acetate and water, and then was dried to obtain product **3** or **4**. Compounds **3c**,**d** and **4c** were additionally purified by column chromatography (silica, eluent: DCM:MeOH, ∼ 20:1).

*4-Benzyl-1-(2-(2-bromophenyl)-4,5-diphenyl-1H-pyrrol-3-yl)-4H-1,2,4-triazol-1-ium Bromide (**3b**).* Compound **3b** (216 mg, 51%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-2-oxoethyl)-4*H*-1,2,4-triazol-1-ium bromide (**1a**) (300 mg, 0.7 mmol), 2,3-diphenyl-2*H*-azirine (**2b**) (200 mg, 1.0 mmol, 1.5 equiv) and triethylamine (42 mg, 0.4 mmol, 0.6 equiv) according to the general procedure A. Colorless solid, mp 237−239 °C. ^{1}H NMR (DMSO-d_6): δ 5.49 (s, 2H), 7.08−7.17 (m, 4H), 7.22−7.43 (m, 12H), 7.44−7.50 (m, 1H), 7.56−7.62 (m, 1H), 7.68−7.77 (m, 1H), 9.38 (s, 1H), 10.49 (s, 1H), 12.44 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 50.6 (CH_2), 116.9 (C), 117.7 (C), 123.3 (C), 127.4 (C), 127.4 (CH), 127.5 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 128.5 (C), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.7 (CH), 130.9 (C), 131.1 (CH), 131.4 (C), 133.0 (CH), 133.0 (CH), 133.8 (C), 144.7 (CH), 145.2 (CH). HRMS (ESI) m/z: 531.1179 calcd for $C_{31}H_{24}BrN_4^+$ [M−Br]$^+$, found 531.1189.

*4-Benzyl-1-(2-(2-bromophenyl)-4-phenyl-5-(pyridin-2-yl)-1H-pyrrol-3-yl)-4H-1,2,4-triazol-1-ium Bromide (**3c**).* Compound **3c** (162 mg, 77%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-2-oxoethyl)-4*H*-1,2,4-triazol-1-ium bromide (**1a**) (150 mg, 0.3 mmol), 2-(3-phenyl-2*H*-azirin-2-yl)pyridine (**2c**) (100 mg, 0.5 mmol, 1.5 equiv), and triethylamine (21 mg, 0.2 mmol, 0.6 equiv) according to the general procedure A. In this case the substance was purified by column chromatography on silica gel using a mixture of DCM and methanol (20:1) as eluent. Yellow solid, mp 142−144 °C. ^{1}H NMR (DMSO-d_6): δ 5.47 (s, 2H), 7.05−7.13 (m, 3H), 7.23−7.28 (m, 3H), 7.32−7.41 (m, 7H), 7.42−7.47 (m, 1H), 7.55−7.59 (m, 1H), 7.62−7.71 (m, 2H), 8.59−8.62 (m, 1H), 9.35 (s, 1H), 10.47 (s, 1H), 12.72 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 50.6 (CH_2), 117.4 (C), 119.6 (C), 120.7 (CH), 122.2 (CH), 123.3 (C), 127.6 (C), 127.7 (CH), 127.7 (CH), 127.9 (CH), 128.4 (C), 128.9 (CH), 128.9 (CH), 129.0 (CH), 129.6 (C), 129.9 (CH), 131.1 (CH), 131.2 (C), 132.7 (CH), 133.1 (CH), 133.7 (C), 136.6 (CH), 144.7 (CH), 145.2 (CH), 149.2 (C), 149.4 (CH). HRMS (ESI) m/z: 532.1131 calcd for $C_{30}H_{23}BrN_5^+$ [M−Br]$^+$, found 532.1132.

*4-Benzyl-1-(4-(2-bromophenyl)-2-phenyl-1H-pyrrol-3-yl)-4H-1,2,4-triazol-1-ium Bromide (**3d**).* Compound **3d** (114 mg, 51%) was obtained from 4-benzyl-1-(2-oxo-2-phenylethyl)-4*H*-1,2,4-triazol-1-ium bromide (**1b**) (150 mg, 0.4 mmol), 3-(2-bromophenyl)-2*H*-azirine (**2d**) (123 mg, 0.6 mmol, 1.5 equiv), and triethylamine (25 mg, 0.3 mmol, 0.6 equiv) according to the general procedure A. The substance was additionally purified by column chromatography on silica gel using a mixture of DCM and methanol (20:1) as eluent, and then was recrystallized from the mixture of methanol, ethyl acetate and diethyl ether. Colorless solid, mp 146−148 °C. ^{1}H NMR (DMSO-d_6): δ 5.53 (s, 2H), 7.17−7.24 (m, 2H), 7.25−7.34 (m, 6H), 7.35−7.45 (m, 6H), 7.58−7.65 (m, 1H), 9.48 (s, 1H), 10.53 (s, 1H), 12.38 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 50.7 (CH_2), 114.1 (C), 118.8 (CH), 120.1 (C), 123.3 (C), 126.5 (CH), 127.7 (C), 127.8 (CH), 127.8 (CH),

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

128.1 (CH), 128.8 (C), 128.9 (CH), 129.0 (CH), 129.0 (CH), 129.5 (CH), 132.2 (CH), 132.4 (C), 132.8 (CH), 133.9 (C), 145.0 (CH), 145.5 (CH). HRMS (ESI) *m/z*: 455.0866 calcd for $C_{25}H_{20}BrN_4^+$ [M−Br]$^+$, found 455.0874.

*1-Benzyl-4-(2-(2-bromophenyl)-4,5-diphenyl-1H-pyrrol-3-yl)-1H-1,2,4-triazol-4-ium Bromide (**4b**).* Compound **4b** (254 mg, 60%) was obtained from 1-benzyl-4-(2-(2-bromophenyl)-2-oxoethyl)-1*H*-1,2,4-triazol-4-ium bromide (**1c**) (300 mg, 0.7 mmol), 2,3-diphenyl-2*H*-azirine (**2b**) (200 mg, 1.0 mmol, 1.5 equiv), and triethylamine (42 mg, 0.4 mmol, 0.6 equiv) according to the general procedure **A**. Colorless solid, mp 242−244 °C. ^{1}H NMR (DMSO-d_6): δ 5.59 (s, 2H), 7.00−7.13 (m, 2H), 7.16−7.23 (m, 2H), 7.26−7.41 (m, 11H), 7.42−7.48 (m, 1H), 7.50−7.57 (m, 1H), 7.62−7.68 (m, 1H), 7.72−7.81 (m, 1H), 9.31 (s, 1H), 10.50 (s, 1H), 12.47 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 54.9 (CH_2), 113.4 (C), 117.7 (C), 123.2 (C), 126.8 (C), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 128.7 (C), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.2 (C), 129.8 (CH), 130.8 (C), 131.2 (C), 131.4 (CH), 133.0 (CH), 133.2 (C), 133.2 (CH), 144.0 (CH), 146.6 (CH). HRMS (ESI) *m/z*: 531.1179 calcd for $C_{31}H_{24}BrN_4^+$ [M−Br]$^+$, found 531.1185.

*1-Benzyl-4-(2-(2-bromophenyl)-4-phenyl-5-(pyridin-2-yl)-1H-pyrrol-3-yl)-1H-1,2,4-triazol-4-ium Bromide (**4c**).* Compound **4c** (750 mg, 88%) was obtained from 1-benzyl-4-(2-(2-bromophenyl)-2-oxoethyl)-1*H*-1,2,4-triazol-4-ium bromide (**1c**) (608 mg, 1.4 mmol), 2-(3-phenyl-2*H*-azirin-2-yl)pyridine (**2c**) (405 mg, 2.1 mmol, 1.5 equiv), and triethylamine (84 mg, 0.8 mmol, 0.6 equiv) according to the general procedure A. In this case the residue obtained after concentration of the reaction mixture was purified by column chromatography on silica gel using a mixture of DCM and methanol (20:1) as eluent. Yellow solid, mp 149−151 °C. ^{1}H NMR (DMSO-d_6): δ 5.58 (s, 2H), 6.99−7.06 (m, 2H), 7.07−7.11 (m, 1H), 7.25−7.29 (m, 1H), 7.30−7.33 (m, 2H), 7.36−7.46 (m, 7H), 7.48−7.54 (m, 1H), 7.61−7.69 (m, 2H), 7.70−7.75 (m, 1H), 8.58−8.65 (m, 1H), 9.32 (s, 1H), 10.52 (s, 1H), 12.76 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 54.9 (CH_2), 113.8 (C), 119.6 (C), 120.6 (CH), 122.2 (CH), 123.1 (C), 127.7 (C), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.8 (CH), 128.9 (CH), 127.9 (C), 129.1 (CH), 129.1 (C), 130.0 (CH), 131.0 (C), 131.4 (CH), 132.8 (CH), 133.1 (C), 133.4 (CH), 136.6 (CH), 144.0 (CH), 146.5 (CH), 149.1 (C), 149.4 (CH). HRMS (ESI) *m/z*: 532.1131 calcd for $C_{30}H_{23}BrN_5^+$ [M−Br]$^+$, found 532.1157.

*1-Benzyl-4-(4-(2-bromophenyl)-2-phenyl-1H-pyrrol-3-yl)-1H-1,2,4-triazol-4-ium Bromide (**4d**).* Compound **4d** (135 mg, 60%) was obtained from 1-benzyl-4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromide (**1d**) (150 mg, 0.4 mmol), 3-(2-bromophenyl)-2*H*-azirine (**2d**) (123 mg, 0.6 mmol, 1.5 equiv), and triethylamine (25 mg, 0.3 mmol, 0.6 equiv) according to the general procedure **A**. Colorless solid, mp 243−245 °C. ^{1}H NMR (DMSO-d_6): δ 5.64 (s, 2H), 7.10−7.20 (m, 2H), 7.28−7.47 (m, 12H), 7.61−7.69 (m, 1H), 9.38 (s, 1H), 10.52 (s, 1H), 12.39 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 54.9 (CH_2), 110.7 (C), 118.8 (CH), 120.1 (C), 123.4 (C), 126.6 (CH), 127.1 (C), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.6 (C), 128.8 (CH), 128.9 (CH), 129.2 (CH), 129.9 (CH), 132.0 (C), 132.8 (CH), 132.8 (CH), 133.3 (C), 144.1 (CH), 146.5 (CH). HRMS (ESI) *m/z*: 455.0866 calcd for $C_{25}H_{20}BrN_4^+$ [M−Br]$^+$, found 455.0883.

*4-(2-(2-Bromophenyl)-4-phenyl-1H-pyrrol-3-yl)-1-methyl-1H-1,2,4-triazol-4-ium Bromide (**4e**).* Compound **4e** (166 mg, 63%) was obtained from 4-(2-(2-bromophenyl)-2-oxoethyl)-1-methyl-1*H*-1,2,4-triazol-4-ium bromide (**1e**) (200 mg, 0.554 mmol), 3-phenyl-2*H*-azirine (**2a**) (97 mg, 0.831 mmol, 1.5 equiv), and triethylamine (40 mg, 0.391 mmol, 0.7 equiv) according to the general procedure **A**. Colorless solid, mp >400 °C. ^{1}H NMR (DMSO-d_6): δ 4.08 (s, 3H), 7.21 (d, J = 7.1 Hz, 2H), 7.24−7.29 (m, 1H), 7.32−7.44 (m, 3H), 7.46 (s, 1H), 7.46−7.56 (m, 2H), 7.73 (d, J = 7.7 Hz, 1H), 9.39 (s, 1H), 10.33 (s, 1H), 12.24 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 39.2 (CH_3), 110.7 (C), 117.4 (CH), 119.7 (C), 123.3 (C), 126.8 (CH), 126.9 (CH), 127.5 (C), 128.1 (CH), 129.0 (CH), 129.6 (C), 131.3 (CH), 131.7 (C), 133.0 (CH), 143.9 (CH), 146.1 (CH). HRMS (ESI) *m/z*: 381.0533 calcd for $C_{19}H_{16}BrN_4^+$ [M−Br]$^+$, found 381.0535.

General Procedure (B) for the Cyclization of Pyrrolyltriazolium Bromides 3 and 4 under Cu-Mediated Conditions. Pyrrolyltriazolium bromide **3** or **4** (1 equiv), 1,10-phenanthroline (1 equiv), K_3PO_4 (2 equiv), and DMF (0.02 mmol/mL) were placed in a flask with screw-cap. Argon was bubbled through the mixture and then CuI (1 equiv) was added. Argon was bubbled through the suspension again and flask was tightly screwed. The reaction mixture was vigorously stirred for 2 or 4 days (for the derivatives of the 4-benzyl-1,2,4−4*H*-triazole and 1-benzyl-1,2,4−1*H*-triazole, respectively) at 50 °C (temperature of oil bath) and then DMF was evaporated under reduced pressure. The solid residue was dissolved in 10 mL of DCM and washed with 5% aq solution of HCl (15 mL) and brine (15 mL). Then DCM solution was dried under Na_2SO_4, filtered, and evaporated to dryness. The residue was subjected to column chromatography on silica gel (DCM/MeOH from 20:1 to 10:1, if other not specified) to obtain the product of cyclization **5** or **15** and triazole-ring-opening product **6**.

General Procedure (C) for the Cyclization of Pyrrolyltriazolium Bromides 3 and 4 under Radical Conditions. Pyrrolyltriazolium bromide **3** or **4** (1 equiv), TTMSS (2−3 equiv), and AIBN (2−3 equiv) in CH_3CN (0.02 mmol/mL) was stirred at 85 °C (temperature of oil bath) for 5 h under argon atmosphere. Then the conversion of starting material was checked by ^{1}H NMR spectrum of an aliquot of the reaction mixture. If the conversion was complete the reaction mixture was evaporated and the residue was purified by column chromatography on silica gel (DCM/MeOH from 30:1 to 20:1). If there was still staring material additional quantity of AIBN and TTMSS was added and the reaction mixture was stirred at 85 °C for 5 h and then worked up as described above. In the case of salts **4** cyclized products **15** were obtained along with debenzylated products **20**.

*1-Benzyl-5-phenyl-1,7-dihydropyrrolo[3,2-c][1,2,4]triazolo[5,1-a]-isoquinolin-4-ium Bromide (**5a**).* Compound **5a** (306 mg, 90%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3a**) (400 mg, 0.746 mmol), TTMSS (553 mg, 2.24 mmol, 3 equiv), and AIBN (489 mg, 2.99 mmol, 3 + 1 equiv) according to the general procedure C. Colorless solid, mp 206−208 °C. ^{1}H NMR (DMSO-d_6): δ 6.26 (s, 2H), 7.34−7.46 (m, 6H), 7.47−7.56 (m, 2H), 7.68−7.75 (m, 1H), 7.80 (d, J = 7.2 Hz, 2H), 8.01 (s, 1H), 8.06−8.15 (m, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 9.64 (s, 1H), 13.42 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 51.3 (CH_2), 111.9 (C), 114.2 (C), 119.0 (C), 121.4 (CH), 122.8 (C), 125.2 (CH), 125.5 (CH), 125.7 (CH), 126.6 (CH), 126.9 (CH), 127.0 (CH), 128.0 (CH), 128.4 (CH), 129.0 (CH), 129.9 (CH), 132.0 (C), 133.3 (CH), 133.4 (C), 138.4 (C), 146.0 (C). HRMS (ESI) *m/z*: 375.1604 calcd for $C_{25}H_{19}N_4^+$ [M−Br]$^+$, found 375.1613.

*1-Benzyl-5,6-diphenyl-1,7-dihydropyrrolo[3,2-c][1,2,4]triazolo-[5,1-a]isoquinolin-4-ium Bromide (**5b**).* Compound **5b** (55 mg, 90%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-4,5-diphenyl-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3b**) (70 mg, 0.114 mmol), TTMSS (99 mg, 0.400 mmol, 2 + 1.5 equiv), and AIBN (66 mg, 0.400 mmol, 2 + 1.5 equiv) according to the general procedure C. Bright yellow solid, mp 171−173 °C. ^{1}H NMR (DMSO-d_6): δ 6.24 (s, 2H), 7.37−7.49 (m, 15H), 7.68−7.73 (m, 1H), 8.10 (m, 1H), 8.46 (d, J = 8.6 Hz, 1H), 8.90 (d, J = 8.3 Hz, 1H), 9.55 (s, 1H), 13.37 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 51.3 (CH_2), 110.8 (C), 111.8 (C), 121.0 (C), 121.9 (CH), 121.9 (C), 125.2 (CH), 125.3 (C), 126.6 (CH), 126.8 (CH), 127.5 (CH), 128.0 (CH), 128.4 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 130.9 (C), 131.6 (CH), 131.9 (C), 133.1 (CH), 133.4 (C), 136.6 (C), 138.2 (C), 146.1 (CH). HRMS (ESI) *m/z*: 451.1917 calcd for $C_{31}H_{23}N_4^+$ [M−Br]$^+$, found 451.1935.

*1-Benzyl-5-phenyl-6-(pyridin-2-yl)-1,7-dihydropyrrolo[3,2-c]-[1,2,4]triazolo[5,1-a]isoquinolin-4-ium Bromide (**5c**).* Compound **5c** (288 mg, 94%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-4-phenyl-5-(pyridin-2-yl)-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3c**) (350 mg, 0.571 mmol), TTMSS (213 mg, 0.858 mmol, 1.5 equiv), and AIBN (186 mg, 1.144 mmol, 2 equiv) according to the general procedure C. Pale yellow solid, mp 172−174 °C. ^{1}H NMR (DMSO-d_6): δ 6.23 (s, 2H), 7.03 (d, J = 8.1 Hz, 1H), 7.34−7.42 (m, 6H), 7.52−7.58 (m, 5H), 7.66−7.76 (m, 2H), 8.06−8.12 (m, 1H),

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

8.46 (d, J = 8.5 Hz, 1H), 8.79 (d, J = 4.1 Hz, 1H), 9.19 (d, J = 8.2 Hz, 1H), 9.52 (s, 1H), 13.66 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 51.3 (CH_2), 112.2 (C), 112.5 (C), 121.0 (C), 122.26 (C), 122.28 (CH), 122.7 (CH), 123.2 (CH), 125.2 (CH), 125.3 (C), 126.7 (CH), 127.3 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.0 (CH), 131.3 (CH), 131.9 (C), 133.2 (CH), 133.3 (C), 134.5 (C), 136.8 (CH), 138.6 (C), 146.2 (CH), 148.9 (C), 149.7 (CH). HRMS (ESI) m/z: 452.1870 calcd for $C_{30}H_{22}N_5^+$ $[M-Br]^+$, found 452.1870.

*1-Benzyl-5-phenyl-1,6-dihydropyrrolo[3,4-c][1,2,4]triazolo[5,1-a]-isoquinolin-4-ium Bromide (**14d**).* Compound **14d** (37 mg, 62%) was obtained from 4-benzyl-1-(4-(2-bromophenyl)-2-phenyl-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3d**) (70 mg, 0.131 mmol), TTMSS (97 mg, 0.392 mmol, 3 equiv), and AIBN (64 mg, 0.392 mmol, 3 equiv) according to the general procedure C. Colorless solid, mp 184−186 °C. ^{1}H NMR (DMSO-d_6): δ 6.19 (s, 2H), 7.36−7.49 (m, 6H), 7.53−7.61 (m, 3H), 7.86 (d, J = 7.2 Hz, 2H), 7.92−7.98 (m, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.38 (d, J = 3.1 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 9.56 (s, 1H), 13.06 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 51.4 (CH_2), 112.9 (C), 113.5 (C), 113.7 (CH), 115.2 (C), 119.2 (C), 123.7 (CH), 125.6 (CH), 126.6 (CH), 126.7 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 129.1 (CH), 129.6 (CH), 129.8 (C), 131.3 (C), 133.2 (C), 133.7 (CH), 140.8 (C), 145.8 (CH). HRMS (ESI) m/z: 375.1604 calcd for $C_{25}H_{19}N_4^+$ $[M-Br]^+$, found 375.1610.

*N-Benzyl-N-(3-phenyl-1H-pyrrolo[3,2-c]isoquinolin-5-yl)-cyanamide (**6a**).* Compound **6a** (103 mg, 98%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3a**) (150 mg, 0.28 mmol), CuI (53 mg, 0.28 mmol, 1 equiv), 1,10-phenanthroline (50 mg, 0.28 mmol, 1 equiv), and K_3PO_4 (119 mg, 0.56 mmol, 2 equiv) according to the general procedure B. Colorless solid, mp 179−180 °C. ^{1}H NMR (DMSO-d_6): δ 5.20 (s, 2H), 7.19−7.25 (m, 1H), 7.29−7.35 (m, 1H), 7.36−7.45 (m, 4H), 7.55−7.60 (m, 2H), 7.66−7.73 (m, 1H), 7.89−7.95 (m, 1H), 8.14 (d, J = 2.8 Hz, 1H), 8.16−8.22 (m, 2H), 8.43−8.49 (m, 2H), 12.54 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 54.9 (CH_2), 115.6 (C), 116.0 (C), 117.1 (C), 121.1 (CH), 122.7 (C), 123.4 (CH), 124.6 (CH), 125.3 (CH), 125.5 (CH), 126.0 (CH), 126.3 (C), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 130.9 (CH), 133.6 (C), 134.3 (C), 135.7 (C), 144.0 (C). HRMS (ESI) m/z: 375.1604 calcd for $C_{25}H_{19}N_4^+$ $[M+H]^+$, found 375.1610.

*N-Benzyl-N-(2,3-diphenyl-1H-pyrrolo[3,2-c]isoquinolin-5-yl)-cyanamide (**6b**).* Compound **6b** (45 mg, 51%) and compound **5b** (44 mg, 42%) were obtained from 4-benzyl-1-(2-(2-bromophenyl)-4,5-diphenyl-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3b**) (120 mg, 0.20 mmol), CuI (37 mg, 0.20 mmol, 1 equiv), 1,10-phenanthroline (35 mg, 0.20 mmol, 1 equiv), and K_3PO_4 (83 mg, 0.39 mmol, 2 equiv) according to the general procedure B. Compound **6b** is colorless solid, mp 232−234 °C. ^{1}H NMR (DMSO-d_6): δ 5.10 (s, 2H), 7.29−7.42 (m, 7H), 7.43−7.48 (m, 2H), 7.50−7.57 (m, 6H), 7.67−7.71 (m, 1H), 7.88−7.96 (m, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.63 (d, J = 8.3 Hz, 1H), 12.50 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 54.7 (CH_2), 114.4 (C), 115.4 (C), 117.5 (C), 121.6 (CH), 122.1 (C), 124.6 (CH), 125.3 (CH), 126.1 (CH), 126.1 (C), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 129.8 (CH), 130.8 (CH), 132.2 (C), 133.4 (C), 135.1 (C), 135.3 (C), 135.6 (C), 144.2 (C). HRMS (ESI) m/z: 451.1917 calcd for $C_{31}H_{23}N_4^+$ $[M+H]^+$, found 451.1924.

*N-Benzyl-N-(3-phenyl-2-(pyridin-2-yl)-1H-pyrrolo[3,2-c]-isoquinolin-5-yl)cyanamide (**6c**).* Compound **6c** (69 mg, 63%) was obtained from 4-benzyl-1-(2-(2-bromophenyl)-4-phenyl-5-(pyridin-2-yl)-1*H*-pyrrol-3-yl)-4*H*-1,2,4-triazol-1-ium bromide (**3c**) (150 mg, 0.245 mmol), CuI (47 mg, 0.245 mmol, 1 equiv), 1,10-phenanthroline (44 mg, 0.245 mmol, 1 equiv), and K_3PO_4 (104 mg, 0.49 mmol, 2 equiv) according to the general procedure B. Colorless solid, mp 223−225 °C. ^{1}H NMR ($CDCl_3$): δ 5.10 (s, 2H), 7.13−7.19 (m, 1H), 7.23−7.32 (m, 3H), 7.42−7.67 (m, 10H), 7.76−7.82 (m, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.60−7.65 (m, 2H), 10.35 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 55.0 (CH_2), 118.2 (C), 118.8 (C), 120.6 (CH), 121.6 (CH), 122.1 (C), 122.2 (CH), 125.3 (CH), 125.6 (CH), 126.1 (C), 127.3 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 130.5 (CH), 130.8 (CH), 131.9 (C), 133.5 (C), 135.5 (C), 136.5 (CH), 136.7 (C), 144.8 (C), 149.1 (CH), 150.0 (C). HRMS (ESI) m/z: 452.1870 calcd for $C_{30}H_{22}N_5^+$ $[M+H]^+$, found 452.1873.

*1-Benzyl-5-phenyl-1,7-dihydropyrrolo[3,2-c][1,2,4]triazolo[3,4-a]-isoquinolin-4-ium Bromide (**15a**).* Compounds **15a** (81 mg, 50%) and **6a** (64 mg, 48%) were obtained from 1-benzyl-4-(2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (**4a**) (190 mg, 0.35 mmol), CuI (68 mg, 0.35 mmol, 1 equiv), 1,10-phenanthroline (64 mg, 0.35 mmol, 1 equiv), and K_3PO_4 (150 mg, 0.71 mmol, 2 equiv) according to the general procedure B. Compound **15a** was recrystallized from a solution of DCM/diethyl ether. Yellow solid, mp 184−187 °C. ^{1}H NMR (DMSO-d_6): δ 6.40 (s, 2H), 7.34−7.41 (m, 5H), 7.49−7.55 (m, 1H), 7.61 (m, 2H), 7.69−7.76 (m, 3H), 7.86 (s, 1H), 8.11 (m, 1H), 8.56 (d, J = 8.5 Hz, 1H), 8.71 (d, J = 8.0 Hz, 1H), 9.28 (s, 1H), 13.55 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 56.3 (CH_2), 110.9 (C), 114.1 (C), 115.4 (C), 121.8 (CH), 124.6 (CH), 126.1 (C), 126.1 (CH), 126.8 (CH), 127.1 (CH), 127.9 (CH), 128.3 (CH), 128.9 (CH), 129.2 (CH), 129.3 (CH), 131.8 (C), 133.5 (C), 133.9 (CH), 134.7 (C), 134.7 (CH), 140.3 (C). HRMS (ESI) m/z: 375.1604 calcd for $C_{25}H_{19}N_4^+$ $[M-Br]^+$, found 375.1615.

Compound **15a** (15 mg, 25%) and product of subsequent debenzylation **20a** (25 mg, 52%) were obtained from 1-benzyl-4-(2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (**4a**) (70 mg, 0.131 mmol), TTMSS (97 mg, 0.392 mmol, 3 equiv) and AIBN (64 mg, 0.392 mmol, 3 equiv) according to the general procedure C.

*1-Benzyl-5,6-diphenyl-1,7-dihydropyrrolo[3,2-c][1,2,4]triazolo-[3,4-a]isoquinolin-4-ium Bromide (**15b**).* Compounds **15b** (87 mg, 84%) and **6b** (12 mg, 14%) were obtained from 1-benzyl-4-(2-(2-bromophenyl)-4,5-diphenyl-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (**4b**) (120 mg, 0.20 mmol), CuI (37 mg, 0.20 mmol, 1 equiv), 1,10-phenanthroline (35 mg, 0.20 mmol, 1 equiv), and K_3PO_4 (83 mg, 0.39 mmol, 2 equiv) according to the general procedure B. Bright yellow solid, mp 202−204 °C. ^{1}H NMR (DMSO-d_6): δ 6.38 (s, 2H), 7.33−7.45 (m, 8H), 7.46−7.53 (m, 2H), 7.54−7.64 (m, 5H), 7.73 (m, 1H), 8.12 (m, 1H), 8.57 (s, J = 8.5 Hz, 1H), 8.65 (s, 1H), 8.88 (d, J = 8.2 Hz, 1H), 13.33 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 56.3 (CH_2), 110.9 (C), 110.9 (C), 117.7 (C), 121.9 (CH), 125.8 (C), 126.2 (CH), 126.8 (CH), 127.0 (CH), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.5 (CH), 130.9 (CH), 131.5 (C), 133.4 (C), 133.7 (CH), 133.7 (C), 133.9 (CH), 135.5 (C), 140.2 (C). HRMS (ESI) m/z: 451.1917 calcd for $C_{31}H_{23}N_4^+$ $[M-Br]^+$, found 451.1904.

Compound **15b** (28 mg, 46%) and product of subsequent debenzylation **20b** (21 mg, 42%) were obtained from 1-benzyl-4-(2-(2-bromophenyl)-4,5-diphenyl-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (**4b**) (70 mg, 0.114 mmol), TTMSS (56 mg, 0.229 mmol, 2 equiv), and AIBN (38 mg, 0.229 mmol, 2 equiv) according to the general procedure C.

*1-Benzyl-5-phenyl-6-(pyridin-2-yl)-1,7-dihydropyrrolo[3,2-c]-[1,2,4]triazolo[3,4-a]isoquinolin-4-ium Bromide (**15c**).* Compounds **15c** (17 mg, 10%) and **6c** (50 mg, 34%) were obtained from 1-benzyl-4-(2-(2-bromophenyl)-4-phenyl-5-(pyridin-2-yl)-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (**4c**) (200 mg, 0.326 mmol), CuI (62 mg, 0.326 mmol, 1 equiv), 1,10-phenanthroline (59 mg, 0.326 mmol, 1 equiv), and K_3PO_4 (138 mg, 0.653 mmol, 2 equiv) according to the general procedure B. Yellow solid, mp 220−222 °C. ^{1}H NMR (DMSO-d_6): δ 6.37 (s, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.32−7.42 (m, 6H), 7.60−7.80 (m, 7H), 8.08−8.16 (m, 1H), 8.48 (s, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.77 (d, J = 4.4 Hz, 1H), 9.14 (d, J = 8.1 Hz, 1H), 13.63 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 56.3 (CH_2), 111.6 (C), 112.3 (C), 117.9 (C), 121.2 (C), 121.6 (CH), 122.7 (CH), 123.2 (CH), 125.7 (C), 126.3 (CH), 126.8 (CH), 127.6 (CH), 128.3 (CH), 128.9 (CH), 129.4 (CH), 130.0 (CH), 130.7 (CH), 131.2 (C), 133.3 (C), 133.4 (C), 133.6 (CH), 134.0 (CH), 136.9 (CH), 140.4 (C), 148.7 (C), 149.7 (CH). HRMS (ESI) m/z: 452.1870 calcd for $C_{30}H_{22}N_5^+$ $[M-Br]^+$, found 452.1858.

*1-Benzyl-5-phenyl-1,6-dihydropyrrolo[3,4-c][1,2,4]triazolo[3,4-a]-isoquinolin-4-ium Bromide (**21d**) and 5-Phenyl-6H-pyrrolo[3,4-c][1,2,4]triazolo[3,4-a]isoquinoline (**22d**).* Compound **21d** (149 mg,

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

53%) and product of subsequent debenzylation **22d** (41 mg, 18%) were obtained from 1-benzyl-4-(4-(2-bromophenyl)-2-phenyl-1*H*-pyrrol-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (**4d**) (330 mg, 0.583 mmol), TTMSS (434 mg, 1.75 mmol, 3 equiv), and AIBN (287 mg, 1.75 mmol, 3 equiv) according to the general procedure C. Compound **21d**, pale yellow solid, mp 213-215 °C. ^{1}H NMR (DMSO-d_6): δ 6.32 (s, 2H), 7.34−7.44 (m, 5H), 7.55−7.70 (m, 4H), 7.77 (d, J = 7.2 Hz, 2H), 7.93−7.99 (m, 1H), 8.29 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 9.29 (s, 1H), 12.92 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 56.4 (CH_2), 111.9 (C), 112.1 (C), 112.6 (C), 113.8 (CH), 119.4 (C), 123.7 (CH), 126.4 (CH), 126.82 (CH), 126.85 (CH), 128.3 (CH), 128.9 (CH), 128.9 (CH), 129.0 (CH), 129.5 (CH), 129.6 (C), 131.3 (C), 133.3 (C), 134.2 (CH), 135.6 (CH), 142.2 (C). HRMS (ESI) m/z: 375.1604 calcd for $C_{25}H_{19}N_4^+$ [M−Br]$^+$, found 375.1612. Compound **22d**, pale violet solid, mp 264−266 °C. ^{1}H NMR (DMSO-d_6): δ 7.47−7.54 (m, 2H), 7.57−7.64 (m, 2H), 7.64−7.72 (m, 3H), 7.95 (d, J = 3.1 Hz, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.45 (d, J = 7.7 Hz, 1H), 8.76 (s, 1H), 12.22 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 111.9 (C), 113.2 (CH), 114.0 (C), 117.9 (C), 118.3 (C), 122.8 (CH), 124.1 (CH), 126.1 (CH), 127.8 (C), 128.2 (CH), 128.9 (CH), 129.1 (CH), 130.3 (CH), 130.8 (C), 135.5 (CH), 147.8 (C). HRMS (ESI) m/z: 285.1135 calcd for $C_{18}H_{13}N_4^+$ [M+H]$^+$, found 285.1142.

*1-Methyl-5-phenyl-1,7-dihydropyrrolo[3,2-c][1,2,4]triazolo[3,4-a]isoquinolin-4-ium Bromide (**15e**).* Compound **15e** (34 mg, 59%) was obtained from 4-(2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-1,2,4-triazol-4-ium bromide (**4e**) (70 mg, 0.146 mmol), TTMSS (109 mg, 0.439 mmol, 3 equiv), and AIBN (72 mg, 0.439 mmol, 3 equiv) according to the general procedure C. Colorless solid, mp 246−247 °C. ^{1}H NMR (DMSO-d_6): δ 4.7 (s, 3H), 7.48−7.54 (m, 1H), 7.57−7.68 (m, 4H), 7.84 (s, 1H), 7.87−7.93 (m, 1H), 8.15−8.21 (m, 1H), 8.64 (d, J = 8.1 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 9.16 (s, 1H), 13.32 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 47.8 (CH_3), 111.8 (C), 114.1 (C), 115.1 (C), 121.27 (C), 121.34 (CH), 124.4 (CH), 125.7 (C), 126.6 (CH), 127.2 (CH), 127.9 (CH), 129.2 (CH), 129.3 (CH), 131.7 (C), 133.7 (CH), 133.8 (CH), 140.3 (C). HRMS (ESI) m/z: 299.1291 calcd for $C_{19}H_{15}N_4^+$ [M−Br]$^+$, found 299.1300.

*General Procedure (D) for Reduction of N-Benzyl-N-(3-phenyl-1H-pyrrolo[3,2-c]isoquinolin-5-yl)cyanamide **6**.* Compound **6** (0.40 mmol) was diluted in the mixture of methanol and 1 M hydrochloric acid (ratio 5:1, 6 mL), 10% Pd/C (10 wt%) was added and the reaction mixture was allowed to stir overnight in the atmosphere of hydrogen at the room temperature. After the reaction was completed, which was monitored by TLC, the mixture was filtered from Pd/C, concentrated *in vacuo*, and partitioned between DCM and sat. aq solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM 3 times, then the organic layers were combined, dried over Na_2SO_4, and filtered off. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (DCM/MeOH 10:1). The obtained solid was washed either with DCM/diethyl ether (**13a**) or with methanol (**13b,c**) to give the pure product.

*3-Phenyl-1H-pyrrolo[3,2-c]isoquinolin-5-amine (**13a**).* Compound **13a** (68 mg, 65%) was obtained from *N*-benzyl-*N*-(3-phenyl-1*H*-pyrrolo[3,2-*c*]isoquinolin-5-yl)cyanamide (**6a**) (150 mg, 0.40 mmol) and Pd/C (9 mg, 10 wt%) according to the general procedure D. Pale yellow solid, mp 194−196 °C. ^{1}H NMR (DMSO-d_6): δ 6.29 (s, 2H), 7.10−7.17 (m, 1H), 7.31−7.43 (m, 3H), 7.65−7.73 (m, 1H), 7.75 (d, J = 3 Hz, 1H), 8.16 (d, J = 8 Hz, 1H), 8.21−8.33 (m, 3H), 11.73 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 114.2 (C), 115.1 (C), 118.7 (C), 119.9 (CH), 120.5 (CH), 123.2 (CH), 124.5 (CH), 125.3 (CH), 125.7 (CH), 126.4 (C), 128.0 (CH), 129.6 (CH), 135.0 (C), 135.8 (C), 152.7 (C). HRMS (ESI) m/z: 260.1182 calcd for $C_{17}H_{14}N_3^+$ [M+H]$^+$, found 260.1175.

*2,3-Diphenyl-1H-pyrrolo[3,2-c]isoquinolin-5-amine (**13b**).* Compound **13b** (46 mg, 84%) was obtained from *N*-benzyl-*N*-(2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]isoquinolin-5-yl)cyanamide (**6b**) (75 mg, 0.17 mmol) and Pd/C (4 mg, 10 wt%) according to the general procedure D. Pale yellow solid, mp 298−300 °C. ^{1}H NMR (DMSO-d_6): δ 6.28 (s, 2H), 7.18−7.26 (m, 1H), 7.27−7.43 (m, 6H), 7.45−7.53 (m, 4H), 7.71 (m, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 8.1 Hz, 1H), 11.71 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 113.4 (C), 115.7 (C), 118.2 (C), 120.5 (CH), 123.3 (CH), 125.3 (CH), 125.4 (CH), 126.3 (C), 127.1 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 129.7 (CH), 130.2 (CH), 132.4 (C), 133.1 (C), 135.1 (C), 136.5 (C), 153.1 (C). HRMS (ESI) m/z: 336.1495 calcd for $C_{23}H_{18}N_3^+$ [M+H]$^+$, found 336.1497.

*3-Phenyl-2-(pyridin-2-yl)-1H-pyrrolo[3,2-c]isoquinolin-5-amine (**13c**).* Compound **13c** (15 mg, 71%) was obtained from *N*-benzyl-*N*-(3-phenyl-2-(pyridin-2-yl)-1*H*-pyrrolo[3,2-*c*]isoquinolin-5-yl)-cyanamide (**6c**) (28 mg, 0.06 mmol) and Pd/C (2 mg, 10 wt%) according to the general procedure D. Pale yellow solid, mp 280−282 °C. ^{1}H NMR (DMSO-d_6): δ 6.26 (s, 2H), 7.15−7.25 (m, 2H), 7.31−7.36 (m, 1H), 7.38−7.45 (m, 3H), 7.46−7.52 (m, 2H), 7.56−7.63 (m, 1H), 7.66−7.73 (m, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.60−8.71 (m, 2H), 11.99 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 115.7 (C), 116.5 (C), 118.8 (C), 121.4 (CH), 121.51 (CH), 121.54 (CH), 123.9 (CH), 125.1 (CH), 126.2 (CH), 126.3 (C), 128.2 (CH), 129.6 (CH), 130.7 (CH), 130.8 (C), 135.2 (C), 136.1 (CH), 137.2 (C), 149.2 (CH), 151.1 (C), 153.3 (C). HRMS (ESI) m/z: 337.1448 calcd for $C_{22}H_{17}N_4^+$ [M+H]$^+$, found 337.1447.

General Procedure (E) for the Synthesis of Pyrrolotriazoloisoquinolines 10 and 16. A suspension of compound **5** or **15** (0.088 mmol) in aq solution of KOH (10 mg, 0.176 mmol, 2 equiv, 5 mL H_2O) was sonicated for 30 min in an ultrasonic bath and then vigorously stirred for 12 h at rt. The precipitate was filtered, washed with water, and thoroughly dried to obtain analytically pure compound **10** or **16** in almost quantitative yield.

*1-Benzyl-5-phenyl-1H-pyrrolo[3,2-c][1,2,4]triazolo[5,1-a]-isoquinoline (**10a**).* Compound **10a** (138 mg, 97%) was obtained from 1-benzyl-5-phenyl-1,7-dihydropyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*]isoquinolin-4-ium bromide (**5a**) (173 mg, 0.38 mmol) and aq solution of KOH (43 mg, 0.76 mmol, 2 equiv) according to the general procedure E. Yellow solid, mp 120−121 °C. ^{1}H NMR (DMSO-d_6): δ 6.18 (s, 2H), 7.16−7.21 (m, 1H), 7.30−7.42 (m, 8H), 7.69 (s, 1H), 7.72−7.77 (m, 1H), 7.79 (d, J = 7.3 Hz, 2H), 8.23 (d, J = 8.6 Hz, 1H), 8.63 (d, J = 8.3 Hz, 1H), 9.46 (s, 1H). Compound **10a** is hardly soluble in DMSO-d_6 and moreover it decomposes in DMSO-d_6 into **6a** especially under heating but all the carbon signals of **10a** can be undoubtedly ascribed if spectrum of mixture with low and high ratio of decomposition and spectrum of **6a** are compared (see SI). ^{13}C NMR (DMSO-d_6): δ 51.0 (CH_2), 108.6 (C), 111.8 (C), 119.6 (C), 121.5 (CH), 123.3 (CH), 124.0 (CH), 124.5 (CH), 126.4 (CH), 127.7 (CH), 128.2 (CH), 128.9 (CH), 129.1 (CH), 130.1 (C), 131.1 (CH), 131.8 (C), 134.1 (C), 134.8 (C), 135.4 (C), 137.4 (CH), 144.9 (CH). HRMS (ESI) m/z: 375.1604 calcd for $C_{25}H_{18}N_4^+$ [M+H]$^+$, found 375.1609.

*1-Benzyl-5,6-diphenyl-1H-pyrrolo[3,2-c][1,2,4]triazolo[5,1-a]-isoquinoline (**10b**).* Compound **10b** (23 mg, 99%) was obtained from 1-benzyl-5,6-diphenyl-1,7-dihydropyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*]-isoquinolin-4-ium bromide (**5b**) (27 mg, 0.051 mmol) and aq solution of KOH (6 mg, 0.101 mmol, 2 equiv) according to the general procedure E. Orange solid, mp 240−243 °C. ^{1}H NMR (DMSO-d_6): δ 6.16 (s, 2H), 7.10−7.16 (m, 1H), 7.18−7.23 (m, 2H), 7.29−7.39 (m, 9H), 7.42−7.46 (m, 2H), 7.53−7.57 (m, 2H), 7.79 (m, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H), 9.35 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 50.9 (CH_2), 108.6 (C), 108.7 (C), 121.6 (CH), 122.1 (C), 123.1 (CH), 124.1 (CH), 125.4 (CH), 125.6 (CH), 126.4 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 129.1 (CH), 130.0 (C), 130.9 (CH), 131.8 (CH), 134.2 (C), 134.4 (C), 136.4 (C), 138.6 (C), 145.1 (CH). HRMS (ESI) m/z: 451.1917 calcd for $C_{31}H_{23}N_4^+$ [M+H]$^+$, found 451.1925.

*1-Benzyl-5-phenyl-6-(pyridin-2-yl)-1H-pyrrolo[3,2-c][1,2,4]-triazolo[5,1-a]isoquinoline (**10c**).* Compound **10c** (14 mg, 87%) was obtained from 1-benzyl-5-phenyl-6-(pyridin-2-yl)-1,7-dihydropyrrolo-[3,2-*c*][1,2,4]triazolo[5,1-*a*]isoquinolin-4-ium bromide (**5c**) (19 mg, 0.036 mmol) and aq solution of KOH (4 mg, 0.072 mmol, 2 equiv) according to the general procedure E. Orange solid, mp 131−132 °C. ^{1}H NMR (DMSO-d_6): δ 6.16 (s, 2H), 7.10−7.16 (m, 1H), 7.23−7.30 (m, 1H), 7.30−7.43 (m, 8H), 7.43−7.50 (m, 2H), 7.62−7.74 (m, 2H), 7.80−7.88 (m, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.39 (d, J = 3.2 Hz, 1H),

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

8.80 (d, J = 7.9 Hz, 1H), 9.36 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 51.0 (CH_2), 109.6 (C), 110.7 (C), 120.9 (CH), 121.76 (C), 121.83 (CH), 122.7 (CH), 124.0 (CH), 124.3 (CH), 125.5 (CH), 126.5 (CH), 127.0 (CH), 128.3 (CH), 128.4 (C), 128.9 (C), 129.1 (CH), 129.5 (C), 130.4 (C), 131.4 (CH), 131.8 (CH), 134.0 (C), 135.5 (C), 135.6 (CH), 145.2 (CH), 148.4 (CH). HRMS (ESI) m/z: 452.1870 calcd for $C_{30}H_{22}N_5^+$ $[M+H]^+$, found 452.1865.

*1-Benzyl-5-phenyl-1H-pyrrolo[3,2-c][1,2,4]triazolo[3,4-a]-isoquinoline (**16a**).* Compound **16a** (33 mg, 99%) was obtained from 1-benzyl-5-phenyl-1,7-dihydropyrrolo[3,2-*c*][1,2,4]triazolo[3,4-*a*]-isoquinolin-4-ium bromide (**15a**) (40 mg, 0.088 mmol) and aq solution of KOH (10 mg, 0.176 mmol, 2 equiv) according to the general procedure E. Yellow solid, mp 162−163 °C. ^{1}H NMR (DMSO-d_6): δ 6.30 (s, 2H), 7.28−7.39 (m, 7H), 7.45−7.54 (m, 3H), 7.59−7.65 (m, 2H), 7.73−7.82 (m, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.50−8.64 (m, 1H), 9.25 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 57.1 (CH_2), 107.3 (C), 112.6 (C), 115.9 (C), 122.8 (CH), 123.6 (CH), 123.8 (CH), 126.4 (CH), 126.5 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 129.6 (CH), 131.3 (C), 132.3 (C), 132.3 (CH), 132.5 (CH), 133.2 (C), 135.8 (C), 138.2 (C). HRMS (ESI) m/z: 375.1604 calcd for $C_{25}H_{19}N_4^+$ $[M+H]^+$, found 375.1600.

*1-Benzyl-5,6-diphenyl-1H-pyrrolo[3,2-c][1,2,4]triazolo[3,4-a]-isoquinoline (**16b**).* Compound **16b** (54 mg, 90%) was obtained from 1-benzyl-5,6-diphenyl-1,7-dihydropyrrolo[3,2-*c*][1,2,4]triazolo[3,4-*a*]-isoquinolin-4-ium bromide (**15b**) (70 mg, 0.132 mmol) and aq solution of KOH (15 mg, 0.264 mmol, 2 equiv, 5 mL H_2O) according to the general procedure E. Yellow solid, mp 185−187 °C. ^{1}H NMR (DMSO-d_6): δ 6.27 (s, 1H), 7.02−7.66 (m, 16H), 7.74−7.84 (m, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H), 8.63 (d, J = 7.9 Hz, 1H). ^{13}C NMR (DMF-d_7): δ 57.4 (CH_2), 109.2 (C), 110.3 (C), 119.7 (C), 122.9 (CH), 124.3 (CH), 126.3 (CH), 126.4 (CH), 127.8 (CH), 128.0 (CH), 128.7 (CH), 128.8 (CH), 129.3 (CH), 130.06 (CH), 130.14 (CH), 130.7 (C), 132.4 (CH), 132.5 (C), 133.0 (CH), 133.2 (CH), 135.6 (C), 138.0 (C), 139.4 (C), 139.8 (C), 145.6 (C). HRMS (ESI) m/z: 451.1917 calcd for $C_{31}H_{23}N_4^+$ $[M+H]^+$, found 451.1908.

General Procedure (F) for Debenzylation of Pyrrolotriazoloisoquinolines 10 and 16. A suspension of Pd/C (10 wt%) compound **10** or **16** (0.035 mmol) in dry methanol (5 mL) was stirred at rt for 12 h under an atmosphere of hydrogen. After the completion of the reaction (monitored by TLC) the reaction mixture was filtered off from Pd/C and evaporated to dryness to give the pure product **31** or **20**.

*5-Phenyl-7H-pyrrolo[3,2-c][1,2,4]triazolo[5,1-a]isoquinoline (**31a**).* Compound **31a** (56 mg, 93%) was obtained from 1-benzyl-5-phenyl-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*]isoquinoline (**10a**) (80 mg, 0.214 mmol) according to the general procedure F. Colorless solid, mp 254−255 °C. ^{1}H NMR (DMSO-d_6): δ 7.30−7.35 (m, 1H), 7.42−7.47 (m, 2H), 7.63−7.68 (m, 1H), 7.69 (d, J = 3.0 Hz, 1H), 7.82−7.88 (m, 1H), 7.87 (d, J = 7.1 Hz, 2H), 8.41 (d, J = 8.2 Hz, 1H), 8.43 (s, 1H), 8.56 (d, J = 7.9 Hz, 1H), 12.76 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 113.8 (C), 117.7 (C), 119.6 (C), 120.3 (C), 120.5 (CH), 122.4 (CH), 123.5 (C), 124.7 (CH), 125.8 (CH), 126.2 (CH), 127.8 (CH), 129.5 (CH), 130.1 (CH), 133.2 (C), 147.0 (C), 151.0 (CH). HRMS (ESI) m/z: 285.1135 calcd for $C_{18}H_{13}N_4^+$ $[M+H]^+$, found 285.1138.

*5,6-Diphenyl-7H-pyrrolo[3,2-c][1,2,4]triazolo[5,1-a]isoquinoline (**31b**).* Compound **31b** (11 mg, 90%) was obtained from 1-benzyl-5,6-diphenyl-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*]isoquinoline (**10b**) (15 mg, 0.033 mmol) according to the general procedure F. Colorless solid, mp 264−266 °C. ^{1}H NMR (DMSO-d_6): δ 7.27−7.48 (m, 10H), 7.60−7.68 (m, 1H), 7.81−7.88 (m, 1H), 8.31 (s, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.63 (d, J = 8.1 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 110.6 (C), 117.9 (C), 119.5 (C), 121.1 (CH), 121.7 (C), 123.3 (C), 124.7 (CH), 125.9 (CH), 126.9 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 130.1 (CH), 131.6 (C), 131.7 (CH), 133.0 (C), 133.3 (C), 147.0 (C), 151.2 (CH). HRMS (ESI) m/z: 383.1267 calcd for $C_{24}H_{16}N_4Na^+$ $[M+Na]^+$, found 383.1249.

*5-Phenyl-6-(pyridin-2-yl)-7H-pyrrolo[3,2-c][1,2,4]triazolo[5,1-a]-isoquinoline (**31c**).* Compound **31c** (5 mg, 71%) was obtained from 1-benzyl-5-phenyl-6-(pyridin-2-yl)-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[5,1-*a*]isoquinoline (**10c**) (9 mg, 0.02 mmol) according to the general procedure F. Colorless solid, mp 226−228 °C. ^{1}H NMR (DMSO-d_6): δ 6.96 (d, J = 8.1 Hz, 1H), 7.25−7.31 (m, 1H), 7.42−7.53 (m, 5H), 7.57−7.64 (m, 1H), 7.64−7.70 (m, 1H), 7.80−7.87 (m, 1H), 8.29 (s, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.72 (d, J = 4.2 Hz, 1H), 8.92 (d, J = 8.2 Hz, 1H), 13.03 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 112.0 (C), 118.4 (C), 120.0 (C), 121.6 (CH), 121.8 (C), 122.0 (CH), 122.3 (CH), 123.3 (C), 124.6 (CH), 126.3 (CH), 127.5 (CH), 128.2 (CH), 130.1 (CH), 131.4 (CH), 131.7 (C), 133.2 (C), 136.4 (CH), 147.0 (C), 149.4 (CH), 149.8 (C), 151.3 (CH). HRMS (ESI) m/z: 384.1220 calcd for $C_{23}H_{15}N_5Na^+$ $[M+Na]^+$, found 384.1233.

*5-Phenyl-7H-pyrrolo[3,2-c][1,2,4]triazolo[3,4-a]isoquinoline (**20a**).* Compound **20a** (9 mg, 90%) was obtained from 1-benzyl-5-phenyl-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[3,4-*a*]isoquinoline (**16a**) (13 mg, 0.035 mmol) according to the general procedure F. Colorless solid, mp 356−357 °C. ^{1}H NMR (DMSO-d_6): δ 7.42−7.48 (m, 1H), 7.50 (s, 1H), 7.56 (m, 2H), 7.59−7.66 (m, 3H), 7.80 (m, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.61 (d, J = 7.9 Hz, 1H), 8.75 (s, 1H), 12.64 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 114.0 (C), 116.3 (C), 117.2 (C), 119.4 (C), 120.4 (CH), 121.2 (CH), 123.4 (C), 124.2 (CH), 126.2 (CH), 127.3 (CH), 128.9 (CH), 129.3 (CH), 130.2 (CH), 133.1 (C), 134.7 (CH), 146.9 (C). HRMS (ESI) m/z: 285.1135 calcd for $C_{18}H_{13}N_4^+$ $[M+H]^+$, found 285.1140.

*5,6-Diphenyl-7H-pyrrolo[3,2-c][1,2,4]triazolo[3,4-a]isoquinoline (**20b**).* Compound **20b** (21 mg, 88%) was obtained from 1-benzyl-5,6-diphenyl-1*H*-pyrrolo[3,2-*c*][1,2,4]triazolo[3,4-*a*]isoquinoline (**16b**) (30 mg, 0.067 mmol) according to the general procedure F. Colorless solid, mp 362−365 °C. ^{1}H NMR (DMSO-d_6): δ 7.28−7.33 (m, 1H), 7.34−7.40 (m, 2H), 7.43−7.48 (m, 2H), 7.49−7.59 (m, 5H), 7.60−7.65 (m, 1H), 7.80−7.85 (m, 1H), 8.14 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.61 (d, J = 7.4 Hz, 1H), 12.59 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 111.0 (C), 117.4 (C), 118.65 (C), 118.68 (C), 121.0 (CH), 123.1 (CH), 124.2 (CH), 126.2 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.5 (CH), 129.2 (CH), 130.2 (CH), 131.0 (CH), 131.3 (C), 131.9 (C), 133.0 (C), 133.8 (C). HRMS (ESI) m/z: 361.1448 calcd for $C_{24}H_{17}N_4^+$ $[M+H]^+$, found 361.1460.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01341.

Photophysical data for selected compounds, NMR spectra for all new compounds and computation details, energies of compounds and their Cartesian coordinates (PDF)

X-ray crystallographic data for **6a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.khlebnikov@spbu.ru

ORCID

Mikhail S. Novikov: 0000-0001-5106-4723

Alexander F. Khlebnikov: 0000-0002-6100-0309

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Russian Science Foundation (Grant No. 16-13-10036). This research was carried out using resources of the X-ray Diffraction Centre, the Centre for Magnetic Resonance, the Computer Centre, the Centre for Optical and Laser Materials Research, and the Centre for Chemical Analysis and Materials of St. Petersburg State University.

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594

REFERENCES

(1) For recent examples see: (a) Santra, M.; Jun, Y. W.; Bae, J.; Sarkar, S.; Choi, W.; Gryko, D. T.; Ahn, K. H. *Asian J. Org. Chem.* **2017**, *6*, 278−281. (b) Ge, Y.; Liu, A.; Dong, J.; Duan, G.; Cao, X.; Li, F. *Sens. Actuators, B* **2017**, *247*, 46−52. (c) Łukasiewicz, Ł. G.; Deperasińska, I.; Poronik, Y. M.; Jun, Y. W.; Banasiewicz, M.; Kozankiewicz, B.; Ahn, K. H.; Gryko, D. T. *Chem. - Asian J.* **2016**, *11*, 1718−1724. (d) Yu, C.; Wu, Q.; Wang, J.; Wei, Y.; Hao, E.; Jiao, L. *J. Org. Chem.* **2016**, *81*, 3761−3770. (e) Sareen, D.; Lee, J. H.; Hwang, H.; Yoo, S.; Lee, C.-H. *Chem. Commun.* **2016**, *52*, 5852−5855. (f) Koshel, E. I.; Tomashenko, O. A.; Khlebnikov, A. F.; Gaginskaya, E. R.; Saifitdinova, A. F.; Tunik, S. P. *Chromosome Res.* **2016**, *24* (1), 29−30. (g) Tomashenko, O. A.; Khlebnikov, A. F.; Mosiagin, I. P.; Novikov, M. S.; Grachova, E. V.; Shakirova, J. R.; Tunik, S. P. *RSC Adv.* **2015**, *5*, 94551−94561. (h) Yang, D.-T.; Radtke, J.; Mellerup, S. K.; Yuan, K.; Wang, X.; Wagner, M.; Wang, S. *Org. Lett.* **2015**, *17*, 2486−2489.

(2) For recent review, see: (a) Ferreira, V. F.; Da Rocha, D. R.; Da Silva, F. R.; Ferreira, F. G.; Boechat, N. A.; Magalhães, J. L. *Expert Opin. Ther. Pat.* **2013**, *23*, 319−331. (b) Maddila, S.; Pagadala, R.; Jonnalagadda, S. B. *Lett. Org. Chem.* **2013**, *10*, 693−714. (c) Thakur, A.; Gupta, P. S.; Shukla, P. K.; Verma, A.; Pathak, P. *Int. J. Curr. Res. Aca. Rev.* **2016**, *4*, 277−296.

(3) Diaz-Ortiz, A.; Prieto, P.; Carrillo, J. R.; Martin, R.; Torres, I. *Curr. Org. Chem.* **2015**, *19*, 568−584.

(4) (a) Dave, C. G.; Shah, P. R. *Molecules* **2002**, *7*, 554−565. (b) Mohamed, M. S.; Rashad, A. E.; Zaki, M. E. A.; Fatahala, S. S. *Acta Pharm.* **2005**, *55*, 237−249. (c) Abdel-Mohsen, S. A. *Bull. Korean Chem. Soc.* **2005**, *26*, 719−728. (d) Vorob'ev, E. V.; Kurbatov, E. S.; Krasnikov, V. V.; Mezheritskii, V. V.; Usova, E. V. *Russ. Chem. Bull.* **2006**, *55*, 1492−1497. (e) Abou El Ella, D. A.; Ghorab, M. M.; Noaman, E.; Heiba, H. I.; Khalil, A. I. *Bioorg. Med. Chem.* **2008**, *16*, 2391−2402. (f) Mohamed, M. S.; Kamel, R.; Fatahala, S. S. *Eur. J. Med. Chem.* **2011**, *46*, 3022−3029. (g) Mohamed, M. S.; Abd El-Hameed, R. H.; Sayed, A. I.; Soror, S. H. *Arch. Pharm.* **2015**, *348*, 194−205.

(5) Baraldi, P. G.; Saponaro, B.; Tabrizi, M. A.; Baraldi, S.; Romagnoli, R.; Moorman, A. R.; Varani, K.; Borea, P. A.; Preti, D. *Bioorg. Med. Chem.* **2012**, *20*, 1046−1059.

(6) Krutošíková, A.; Kováč, J.; Dandárová, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 65−70.

(7) Friedman, M.; Frank, K. E.; Aguirre, A.; Argiriadi, M. A.; Davis, H.; Edmunds, J. J.; George, D. M.; George, S. J.; Goedken, E.; Fiamengo, B.; Hyland, D.; Li, B.; Murtaza, A.; Morytko, M.; Somal, G.; Stewart, K.; Tarcsa, E.; Van Epps, S.; Voss, J.; Wang, L.; Woller, K.; Wishart, N. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4399−4404.

(8) Sato, Y.; Shimoji, Y.; Fujita, H.; Nishino, H.; Mizuno, H.; Kobayashi, S.; Kumakura, S. *J. Med. Chem.* **1980**, *23*, 927−937.

(9) Funt, L. D.; Tomashenko, O. A.; Khlebnikov, A. F.; Novikov, M. S.; Ivanov, A. Yu. *J. Org. Chem.* **2016**, *81*, 11210−11221.

(10) Khlebnikov, A. F.; Golovkina, M. V.; Novikov, M. S.; Yufit, D. S. *Org. Lett.* **2012**, *14*, 3768−3771.

(11) Tomashenko, O. A.; Novikov, M. S.; Khlebnikov, A. F. *J. Org. Chem.* **2017**, *82*, 616−623.

(12) (a) Jamal, Z.; Teo, Y.-C. *RSC Adv.* **2016**, *6*, 75449−75452. (b) Tadikonda, R.; Nakka, M.; Rayavarapu, S.; Kalidindi, S. P. K.; Vidavalur, S. *Tetrahedron Lett.* **2015**, *56*, 690−692. (c) Huang, Y.; Chen, W.; Zhao, D.; Chen, C.; Yin, H.; Zheng, L.; Jin, M.; Han, S. *Chin. J. Chem.* **2013**, *31*, 1007−1010. (d) Barbero, N.; SanMartin, R.; Dominguez, E. *Org. Biomol. Chem.* **2010**, *8*, 841−845. (e) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura. *Org. Lett.* **2009**, *11*, 3072−3075. (f) Do, H.-Q.; Kashir Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185−15192.

(13) (a) Konyukhov, V. N.; Dianova, L. N.; Koksharova, T. G.; Volkova, N. V.; Bakulev, V. A.; Anisimova, O. S. *Chem. Heterocycl. Compd.* **1985**, *21*, 355−358. (b) Paponov, B. V.; Shihkin, O. V.; Shishkina, S. V.; Kovach, Y. A.; Kravchenko, S. A.; Doroshenko, A. O. *Monatsh. Chem.* **2009**, *140*, 1337−1342.

(14) Pellei, M.; Gandin, V.; Marinelli, M.; Orsetti, A.; Del Bello, F.; Santini, C.; Marzano, C. *Dalton Trans.* **2015**, *44*, 21041−21052.

(15) Fraser, R. R.; Mansour, T. S.; Savard, S. *Can. J. Chem.* **1985**, *63*, 3505−3509.

(16) Daugulis, O. *Top. Curr. Chem.* **2009**, *292*, 57−84.

(17) Grychowska, K.; Satała, G.; Kos, T.; Partyka, A.; Colacino, E.; Chaumont-Dubel, S.; Bantreil, X.; Wesołowska, A.; Pawłowski, M.; Martinez, J.; Marin, P.; Subra, G.; Bojarski, A. J.; Lamaty, F.; Popik, P.; Zajdel, P. *ACS Chem. Neurosci.* **2016**, *7*, 972−983.

DOI: 10.1021/acs.joc.7b01341
J. Org. Chem. 2017, 82, 7583−7594