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A PASE-based approach towards 12-(1*H*-1,2,3-triazol-1-yl)-indolo[2,1-*a*]isoquinolines *via* the reaction of 3-(isoquinolin-1-yl)-1,2,4-triazines with benzyne

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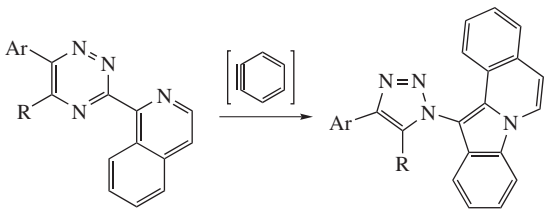
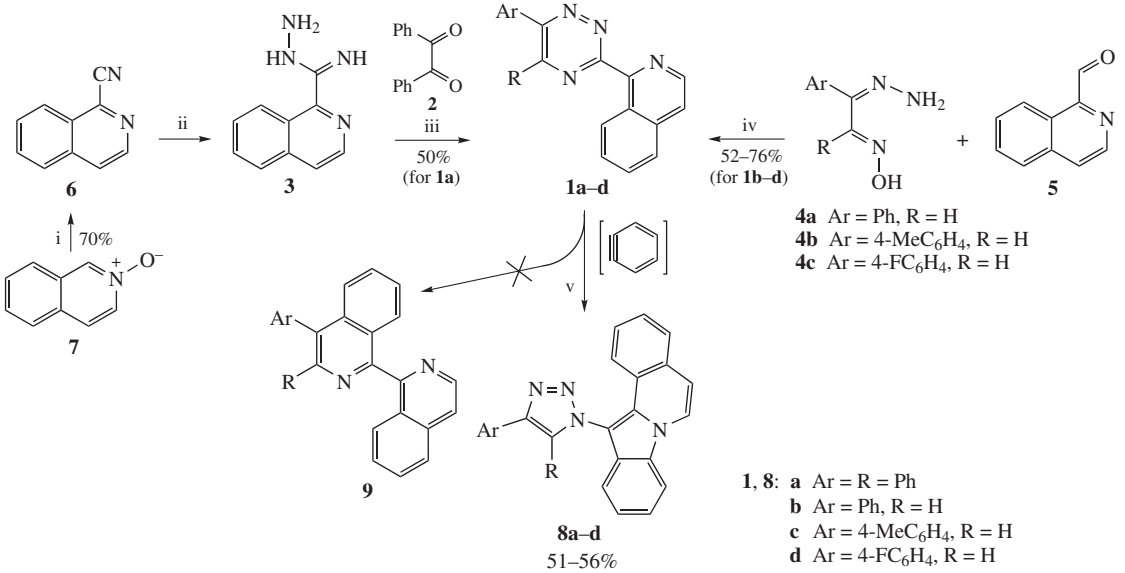
12-(1*H*-1,2,3-Triazol-1-yl)indolo[2,1-*a*]isoquinolines are prepared in 51–56% yields using a PASE (pot, atom, step, economic)-based approach, namely, by the reaction between available 5-R-6-Ar-3-(isoquinolin-1-yl)-1,2,4-triazines and *in situ* generated benzyne. A mechanism comprising domino-transformation was suggested, and the structure of one key product was confirmed by a single crystal X-ray diffraction analysis.



Domino transformations

Indolo[2,1-*a*]isoquinoline core and its isosters are widely present in alkaloids, and both the synthetic and natural indolo[2,1-*a*]-isoquinolines exhibit activities of estrogen receptor affinic cytostatic agents[1] or modulators,[2] tubulin-binding drugs in cancer therapy,[3] and some other activities.[4,5] Additionally, some indolo-[2,1-*a*]isoquinolines are reported as organic semiconductors.[6] The most common approaches to indolo[2,1-*a*]isoquinolines are based on multistage schemes, for instance, metal-catalyzed constructing an isoquinoline core above the indole one[7–17] as well as various heterocyclizations,[18–22] and other transformations.[23–26]

On the other hand, aryne intermediates are the prospective reagents to be used in synthetic organic chemistry,[26] chemistry of materials[27] and drugs.[28] Namely, reactions of arynes with substituted 1,2,4-triazines or 1,2,4,5-tetrazines allow one to obtain isoquinolines,[29] 2-azaanthracenes[30] and their aza-analogues (azaquinolines).[31] Apart from that, we reported previously the



Scheme 1 *Reagents and conditions*: i, KCN, Me_3SiCl, NEt_3, DMF, 50 °C, 16 h; ii, $H_2NNH_2 \cdot H_2O$, EtOH, 20 °C, 96 h; iii, EtOH–THF (1:1), reflux, 10 h; iv, AcOH, 20 °C, 20 h; v, 2-$H_2NC_6H_4CO_2H$, $Me_2CH(CH_2)_2ONO$, toluene–1,4-dioxane (2.5:1), reflux, 1.5 h.

formation of 10-(1*H*-1,2,3-triazol-1-yl)pyrimido-[32] and 10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles,[33] including polyfluorinated ones,[34] as a result of the domino-transformation of 3-[(aza)-pyridin-2-yl]-1,2,4-triazines under the action of (fluoro)arynes. It was found that 2-pyri(mi)dine fragment at the C(3) position of 1,2,4-triazines plays a crucial role in the formation of domino-products. Therefore, to investigate the influence of the benzene ring annulation in the 2-pyridyl substituent in 1,2,4-triazines on the reaction pathway, here we studied the reactions of 3-(isoquinolin-1-yl)-1,2,4-triazines with *in situ* generated benzyne.

To prepare the starting 1,2,4-triazines **1**, two synthetic approaches were used (Scheme 1). The first one comprises the known procedure[35] involving benzil **2** and amidrazone **3** to afford 1,2,4-triazine **1a** in 50% yield. The second one is based on the cyclocondensation between hydrazone **4** and isoquinoline-1-carbaldehyde **5**[36] to result in 1,2,4-triazines **1b–d** in up to 61% yields (see Scheme 1). For the synthesis of amidrazone **3**, a reported method[35] involving the prolonged treatment of 1-cyanoisoquinoline **6** with a large excess of hydrazine hydrate was employed. 1-Cyanoisoquinoline **6**, in turn, was prepared from the corresponding *N*-oxide **7** and Me_3SiCN generated *in situ* from potassium cyanide and Me_3SiCl. This method was used earlier for the cyanation reaction in (benzo[*h*])quinoline oxides.[37] To obtain 1,2,4-triazines **1b–d**, the condensation between hydrazone **4** and aldehyde **5** was carried out in glacial acetic acid, as it was previously suggested,[38] while the attempted reaction between **4** and **5** in ethanol[39,40] afforded only a non-identified mixture of several products.

The reaction between 1,2,4-triazines **1** and benzyne was performed typically[33] when benzyne was generated *in situ* from 2-aminobenzoic acid and isoamyl nitrite in refluxing toluene/1,4-dioxane mixture. As a result, domino products, namely 12-(1*H*-1,2,3-triazol-1-yl)indolo[2,1-*a*]isoquinolines **8**, were isolated in 51–56% yields, whereas the possible isoquinolines **9** were not formed at all. The structure of representative compound **8a** was ultimately confirmed by X-ray diffraction analysis (Figure 1).†

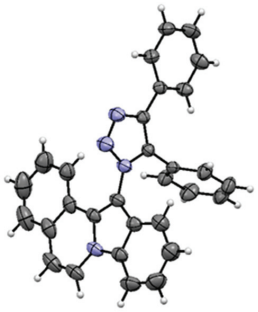


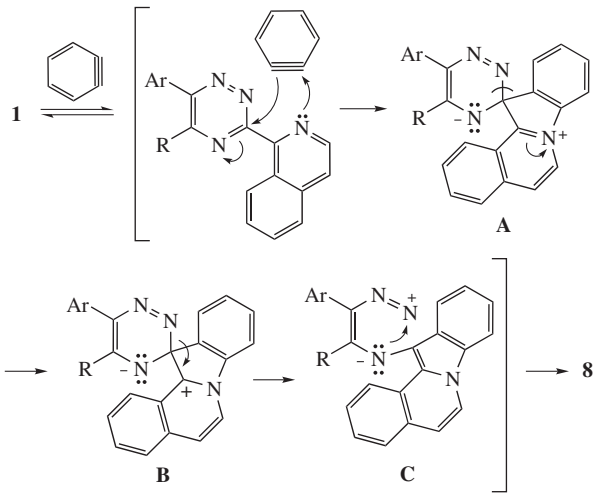
Figure 1 Single crystal X-ray structure of compound **8a**.

† *Crystal data for* **8a**. Crystals of $C_{30}H_{20}N_4$ (M = 436.50) are monoclinic, space group $P2_1/c$, a = 13.2659(11), b = 12.4205(6) and c = 14.6024(12) Å, β = 111.610(8)°, V = 2236.9(3) Å^3, Z = 4, μ(MoKα) = 0.078 mm^{-1}. On the angles 2.84 < θ < 33.24°, 32849 reflections measured, 7409 unique (R_{int} = 0.0442) and 3603 with $I > 2\sigma(I)$ which were used in all calculations. The final R_1 = 0.1222, wR_2 = 0.1205 (all data) and R_1 = 0.0496, wR_2 = = 0.1078 [$I > 2\sigma(I)$], GOOF = 1.002. Largest diff. peak and hole 0.225 and –0.182 e Å^{-3}. The XRD analysis was accomplished on an Xcalibur 3 diffractometer using standard procedure [MoKα-irradiation, graphite monochromator, ω-scans with 1° step, 295(2) K]. Using Olex2,[41] the structure was solved with the ShelXS[42] structure solution program using Direct Methods and refined with the ShelXL[42] refinement package using Least Squares minimization in anisotropic approximation for the nonhydrogen atoms. The H-atoms were added in the calculated positions and were refined using the riding model in the isotropic approximation.

CCDC 1861705 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Compound **8a** is crystallized in the centrosymmetric space group. The molecule is non-planar. The phenyl substituent at the position of C(4) is placed approximately parallel to the plane of the triazole ring, while the phenyl substituent at C(5) is turned toward triazole at the angle of 79° and the whole tetracyclic system is turned toward triazole moiety at the angle of 81°. The bond distances and angles in the molecule are close to the standard values. No any significantly shortened intermolecular contacts or π–π-stacking in a crystal are observed.

The rational mechanism for the transformation is similar to the previously reported ones[30,32] (Scheme 2) and involves a concerted or stepwise addition of *in situ* generated benzyne at the C(3) carbon atom of the 1,2,4-triazine ring and the nitrogen atom of the isoquinoline substituent to afford the intermediate **A**. A further isomerization of **A** leads to intermediate **B**, which would further rearrange *via* the open-chained intermediate **C** into the final indolo[2,1-*a*]isoquinoline **8**.



Scheme 2

In conclusion, a PASE-based approach towards 12-(1*H*-1,2,3-triazol-1-yl)indolo[2,1-*a*]isoquinolines *via* benzyne-mediated domino transformation of easily available 3-(isoquinolin-1-yl)-1,2,4-triazines has been elaborated. The resulting compounds seem promising for multipurpose applications.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.002.

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