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2-Aminooxazoles as novel dienophiles in the inverse demand Diels–Alder reaction with 1,2,4-triazines

Alexey P. Krinochkin,[a,b] Guda Mallikarjuna Reddy,[a] Dmitry S. Kopchuk,*[a,b] Pavel A. Slepukhin,[a,b] Yaroslav K. Shtaitz,[a] Igor A. Khalymbadzha,[a,b] Igor S. Kovalev,[a] Grigory A. Kim,[a,b] Ilya N. Ganebnykh,[b] Grigory V. Zyryanov,[a,b] Oleg N. Chupakhin[a,b] and Valery N. Charushin[a,b]

[a] *Institute of Chemical Engineering, Ural Federal University, 620002 Ekaterinburg, Russian Federation*
[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences,*
620990 Ekaterinburg, Russian Federation. Fax: +7 343 374 1189; e-mail: dkopchuk@mail.ru

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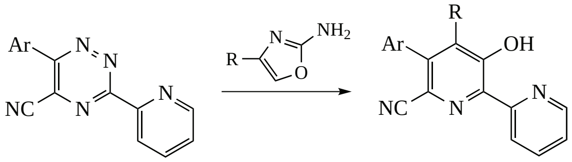
High temperature coupling of 6-aryl-5-cyano-3-(pyridin-2-yl)-1,2,4-triazines with 2-amino-4-aryloxazoles proceeds as the inverse demand Diels–Alder reaction between the oxazole moiety as dienophile and the 1,2,4-triazine moiety as diene to construct new 4,5-diaryl-6-cyano-3-hydroxypyridin-2-yl fragment. A reaction mechanism is proposed, and the structure of the key-product is proved by the X-ray diffraction analysis.

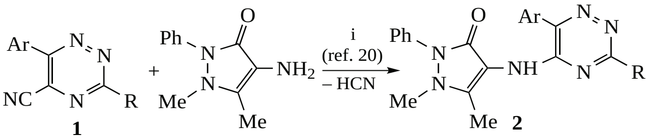


Keywords: 1,2,4-triazines, oxazol-2-amines, inverse electron demand reactions, Diels–Alder reaction, 2,2′-bipyridin-3-ols, solvent-free reactions.

The inverse electron demand (IED) Diels–Alder reactions in a series of 1,2,4-triazines are an effective method for producing a variety of multi-substituted pyridines based on 1,2,4-triazine precursors.[1,2] The 1,2,4-triazine nucleus can be subjected to wide range of pre-functionalizations including *ipso*-substitution reactions or direct C–H functionalization.[3–7] Additional functionalization of positions 3 and 4 of the new pyridine ring fused with cycloalkene[8–10] or benzene rings,[11–13] or bearing aromatic substituents[14] and others is possible. 2,5-Norbornadiene,[3–7] enamines,[8–10] aryne intermediates[11–13] or arylacetylenes[14] can be applied as dienophiles in the aza-Diels–Alder reaction.

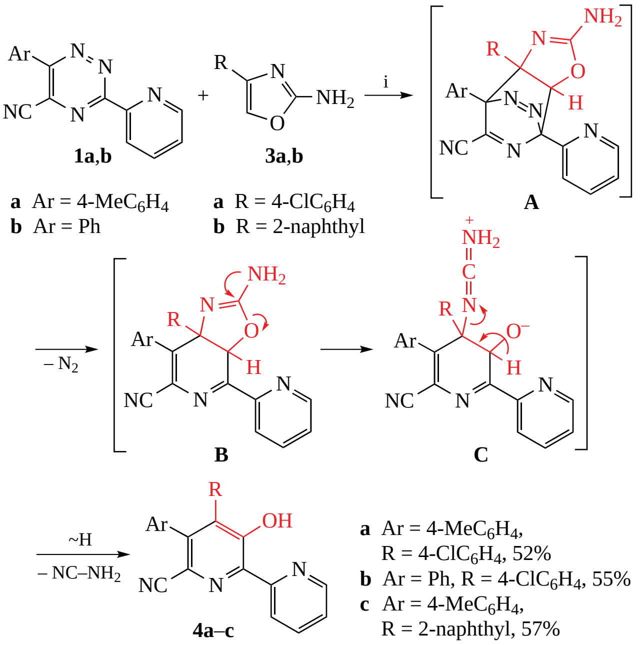
It was previously shown that C^5-cyano group in 1,2,4-triazines of type **1** (Scheme 1) is very labile and can be *ipso*-replaced with various nucleophiles such as C–H active compounds,[15,16] alcohols,[17,18] amines,[19–21] or organolithium compounds.[22,23] Such a functionalization of the 1,2,4-triazine core was employed to construct 2,2′-bipyridine ligands for possible application in non-linear optics.[24–29] When anilines[26–28] or 4-aminoantipyrine[20] (see Scheme 1) were used as the nucleophiles, the reaction could be readily carried out as a solvent-free process at 150 °C.

In this article, we report on an atypical transformation of 6-aryl-3-(pyridin-2-yl)-1,2,4-triazine-5-carbonitriles of type **1** (see Scheme 1) in the course of reaction with 2-amino-4-aryloxazoles **3** (Scheme 2) when the latter were used in place of other amines (*cf*. refs. 20, 26–28). In this case, the expected products of the *ipso*-substitution of the C^5-cyano group in the 1,2,4-triazine core of type **2** (see Scheme 1) were not formed. The ^{1}H NMR spectra of the obtained products contained the extremely downfield broad singlet whereas the typical signal for the C^5-positioned oxazole proton was not observed. The mass spectrometry data (see Online Supplementary Materials, Figures S1–S3) did not conform with the structure of the



Ar = 4-XC_6H_4 (X = H, Br, Me, MeO)
R = Ar or pyridin-2-yl

Scheme 1 *Reagents and conditions*: i, neat, 150 °C, 8 h.



Scheme 2 *Reagents and conditions*: i, neat, 150 °C, 8 h.

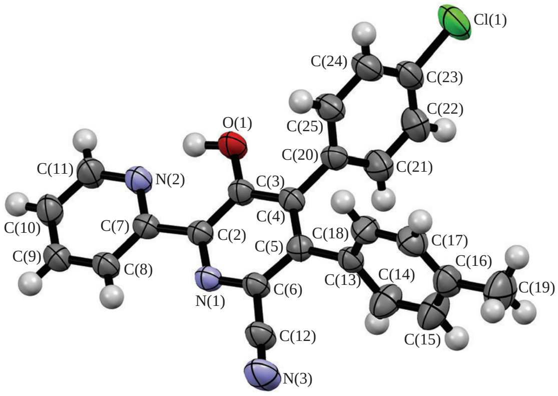


Figure 1 X-ray structure of compound **4a**.

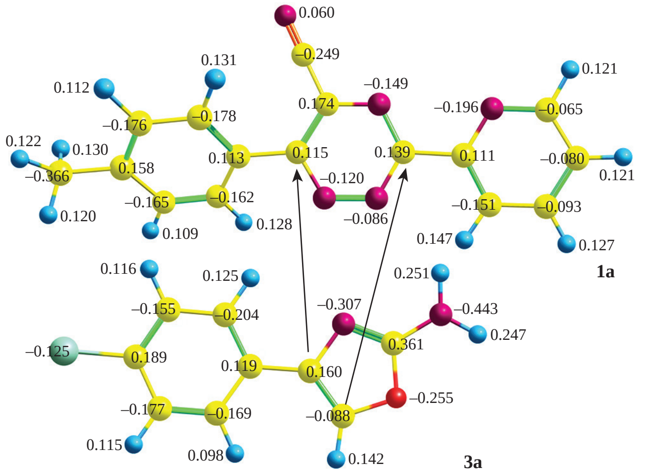


Figure 2 Calculated Mulliken atomic charges for molecules of **1a** and **3a**.

products of type **2**. The ultimate elucidation of the structure of the obtained compounds as 4,5-diaryl-3-hydroxy-2,2′-bipyridine-6-carbonitriles was derived from X-ray diffraction data for compound **4a** as an example (Figure 1).†

The molecule of **4a** is crystallized in the general position. The bond distances and angles are near to standard. The bipyridine part of the molecule is planar with *s-trans* placed nitrogen atoms. This conformation was fixed by intramolecular H-bond O(1)–H(1)···N(2) with d[O(1)–H(1)] = 0.99(5) Å, d[H(1)···N(2)] = 1.65(5) Å, ∠DHA = 146(2)°. The aryl substitutes were turned on the high angles (68 and 72°) toward plane of the heterocyclic moiety. In the crystal, there are shortened (polar) intermolecular contacts O(1)···H(11A) [1–*x*, *y*, 2.5–*z*] 2.513 Å and CN(3)···H(9A) [1–*x*, *y*, 3.5–*z*] 2.658 Å which are responsible for the layered packing of the molecules.

A proposed mechanism for the reaction is presented in Scheme 2. At the first stage, the cycloaddition of aminooxazole **3** as the dienophile takes place at the C^3 and C^6 positions of the 1,2,4-triazine core (structure **A**). Further elimination of nitrogen molecule results in a sterically strained structure **B**. Next, cleavage of the O–C bond occurs, and the oxazole ring opening affords intermediate **C**. The elimination of cyanamide molecule and proton transfer leads to the final pyridines **4**.

We have attempted to explain the regioselectivity of the addition of oxazole to the 1,2,4-triazine fragment. Firstly, we have carried out quantum-chemical calculations of the frontier molecular orbitals of two reacting compounds, namely **1a** and **2a**. However, the results of these calculations showed no significant differences in the localization of LUMO and HOMO at the C^3 and C^6 positions of 1,2,4-triazine (see Online Supplementary Materials, Figure S2), and this result rules out the orbital control of the reaction. On the other hand, our calculations of the Mulliken atomic charges for molecules **1a** and **3a** revealed a significant difference in these values for the C^4 and C^5 atoms of 2-aminooxazole **3a** and C^3 and C^6 atoms of 1,2,4-triazine **1a**, respectively (Figure 2). So, one may suggest that the reaction between **1a** and **3a** proceeds under the charge control.

Literature analysis showed that the herein reported transformation of 1,2,4-triazine is a rare case when the substituted oxazole acted as a dienophile in the Diels–Alder/retro-Diels–Alder reaction sequence, and is documented only in few cases.[33,34] More typically, oxazoles act as dienes in the Diels–Alder reaction with the formation of substituted pyridines by a different mechanisms.[35–38] It should also be noted that there are no examples of similar reactions of oxazoles with 1,2,4-triazines whereas a single analogous case for 1,2,4,5-tetrazine is known.[39]

It is worth mentioning that 2,2′-bipyridin-3-ols are of interest for their biological activity as antineoplastic agents,[40] inhibitors of IKK-beta[41] and human jurkat T cells inhibitors.[42] The structural similarity of bipyridines **4** and dipyrimicins A and B[43,44] (see Online Supplementary Materials, Figure S1) which were recently isolated from the cultures of *Amycolatopsis* bacteria and exhibited antimicrobial and cytotoxic activity should be of note.

In conclusion, few examples of rare transformation of 1,2,4-triazines into 3-hydroxy-2,2′-bipyridine-6-carbonitriles which can be of interest as promising biological candidates have been reported. Their synthesis is based on the solvent-free reaction between 3-(pyridin-2-yl)-1,2,4-triazine-5-carbonitriles and 2-amino-4-aryloxazoles, when instead of the expected *ipso*-substitution of the C^5 cyano group in the 1,2,4-triazine core by the oxazole amino group the inverse electron demand Diels–Alder/retro-Diels–Alder reaction sequence takes place between oxazole as a dienophile and 1,2,4-triazine as a diene.

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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.2021.07.035.

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† *Crystal data for* **4a**. $C_{24}H_{16}N_3OCl$ (M = 397.85), monoclinic, space group $C2/c$ at 295(2) K: a = 21.684(3), b = 16.983(2) and c = 15.1515(17) Å, β = 133.792(11)°, V = 4027.7(10) Å^3, Z = 8, d_{calc} = 1.312 g cm^{-3}, μ(MoKα) = 0.210 mm^{-1}, F(000) = 1648. On the angles 7.208° ⩽ 2θ ⩽ 56.558° total of 13432 reflections were collected (4936 independent reflections, R_{int} = 0.0621, R_{sigma} = 0.0779) which were used in all calculations. The final R_1 = 0.0626, wR_2 = 0.1583 [for reflections with $I > 2\sigma(I)$] and R_1 = 0.1443, wR_2 = 0.2234 (for all data), GOOF = 1.000. Largest diff. peak and hole 0.24/–0.30 $\bar{e}$Å^{-3}.

The XRD experiment was accomplished on equipment of the ‘SAOC’ centre of collective using IOS UB RAS with using the automated ‘Xcalibur 3’ diffractometer on standard procedure (MoK-irradiation, graphite monochromator, ω-scans with 1° step). Empirical absorption correction was applied. The collection, data reductions and refinement of the unit cell parameters were carried out using the CrysAlisPro program.[31] The structures were solved with the ShelXS structure solution program using direct method and refined with the ShelXL[32] refinement program using Least Squares minimization in anisotropic approximation for non-hydrogen atoms. The H-atoms at the CH-bonds were added in the calculated positions and refined isotropically in the ‘rider’ model; an H-atom of the OH-group was refined independently.

CCDC 2000842 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.

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