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Synthesis of 4- and 3-aminopyridines from 1,2,4-triazines and 2-aminooxazole by the ring opening of oxazole cycloadducts

Evgeny D. Ladin,*[a,b] Anastasiya S. Alekseeva,[a,c] Pavel A. Slepukhin,[a,b] Ekaterina A. Kudryashova,[a,b] Anastasiya V. Rybakova,[d] Vladimir V. Chernyshov,[c] Dmitry S. Kopchuk[a,b] and Grigory V. Zyryanov[a,b]

[a] *Institute of Chemical Engineering, Ural Federal University, 620002 Ekaterinburg, Russian Federation. E-mail: ladin.evgenij@yandex.ru*

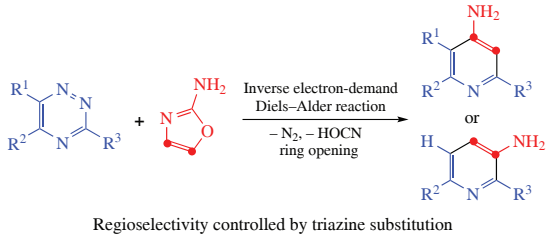
[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620219 Ekaterinburg, Russian Federation*

[c] *Moscow Institute of Physics and Technology (National Research University), 141701 Dolgoprudny, Moscow Region, Russian Federation*

[d] *Institute of Natural and Exact Sciences, South Ural State University, 454080 Chelyabinsk, Russian Federation*

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The C^4=C^5 double bond of 2-aminooxazole serves as dienophile in the course of inverse electron-demand Diels–Alder reactions with 1,2,4-triazines. The primary tricyclic adducts would lose dinitrogen molecule to form fused oxazolopyridine core whose aminooxazoline moiety undergoes extrusion of HOCN species, which finally leads to 3- or 4-aminopyridines. The regioselectivity of the process is governed by the substitution pattern of the triazine core.



Regioselectivity controlled by triazine substitution

Keywords: 1,2,4-triazines, 2-aminooxazole, inverse electron-demand Diels–Alder reactions, oxazoles, cycloadducts, aminopyridines.

The inverse electron-demand Diels–Alder (IEDDA) reaction of 1,2,4-triazines with electron-rich dienophiles represents a powerful approach to substituted pyridines.[1] In addition to enamines and other electron-rich alkenes,[2–7] heterocyclic dienophiles have attracted particular attention, as they enable access to both functionalized pyridines and heteroannulated systems.[8–13]

Previously, we demonstrated that reactions of 2-amino-4-aryloxazoles with 1,2,4-triazines afforded structurally diverse pyridines depending on the substitution pattern of the triazine core.[11–13] However, the reactivity of unsubstituted 2-aminooxazole in such reaction has not been investigated. Herein, we report an alternative oxazole-derived cycloadduct ring-opening pathway observed in the IEDDA reactions between unsubstituted 2-aminooxazole with 1,2,4-triazines, leading to aminopyridines.

In fact, the reactions of substituted 1,2,4-triazines **1a–h** with unsubstituted 2-aminooxazole **2** upon heating in *o*-xylene at 150 °C afforded 4-aminopyridines **3a–h** (Scheme 1). The yields were moderate (36–56%, products **3a–f**) or even low but admissible (12–20%, products **3g**,**h**). The ^{1}H NMR spectra of compounds **3** exhibit signals for the amino group at 4.1–4.5 ppm (*cf.* ref. 14) as well as a singlets at 7.7–7.9 ppm corresponding to the 3-positioned proton of the newly formed pyridine ring. The crystal structure of **3a** as the solvate of a dimeric cadmium complex, $(\mathbf{3a}\cdot CdI_2)_2\cdot 2MeCN$, was confirmed by X-ray diffraction analysis (Figure 1).†

A plausible mechanism for the reaction is outlined in Scheme 1. The process is initiated by an inverse electron-demand Diels–Alder cycloaddition of 2-aminooxazole **2**, acting as an electron-rich dienophile, to the 1,2,4-triazine ring at the C^3 and C^6 positions, followed by extrusion of molecular nitrogen to give intermediate **A**. Subsequent cleavage of the O–C bond of the oxazole fragment results in ring opening and formation of intermediate **B**. Formal elimination of cyanic acid from **B** affords the final aminopyridines **3**. Notably, the regioselectivity of the cycloaddition of 2-aminooxazole to the 1,2,4-triazine core is consistent with that observed previously for related systems.[11]

Attempts to extend the reaction to 5-unsubstituted 1,2,4-triazines resulted in complex mixtures and only traces of the desired products.

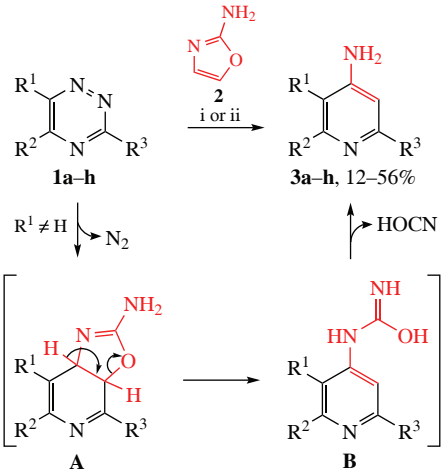
In the case of 6-unsubstituted 1,2,4-triazines **4a**,**b**, the cycloaddition appears to proceed with inverted regio-

† *Crystal data for* $(\mathbf{3a}\cdot CdI_2)_2\cdot 2MeCN$. [Monomeric unit $C_{20}H_{17}CdI_2N_5$ (M = 693.59)] triclinic, space group $P\bar{1}$, a = 8.9742(5), b = 9.1039(5) and c = 15.3620(9) Å, α = 102.899(5)°, β = 105.579(5)°, γ = 94.829(5)°, V = 1164.49(12) Å^3, Z = 2, d_{calc} = 1.978 g cm^{-3}, $F(000)$ = 652.0, T = 295 K, μ(MoKα) = 3.603 mm^{-1}, θ_{min} = 2.32°, θ_{max} = 30.49°, 9220 reflections measured, 6205 independent reflections (R_{int} = 0.0221), R_1 = 0.0382, wR_2 = 0.0678 for 4563 reflections with $I > 2\sigma(I)$; R_1 = 0.0616, wR_2 = 0.0776 for all data, GOF = 1.011, ρ_{max}/ρ_{min} = 0.525/-0.992 e Å^{-3}.

Crystal data for **5a**. $C_{16}H_{12}ClN_3$ (M = 281.74), monoclinic, space group $I2y$, a = 13.0171(6), b = 5.3893(3) and c = 19.6118(12) Å, β = 95.507(5)°, V = 1369.48(13) Å^3, Z = 4, d_{calc} = 1.367 g cm^{-3}, $F(000)$ = 584.0, T = 295 K, μ(MoKα) = 0.271 mm^{-1}, θ_{min} = 2.086°, θ_{max} = 30.623°, 4956 reflections measured, 3217 independent reflections (R_{int} = 0.0207), R_1 = 0.0470, wR_2 = 0.0838 for 1802 reflections with $I > 2\sigma(I)$; R_1 = 0.1065, wR_2 = 0.1107 for all data, GOF = 1.003, ρ_{max}/ρ_{min} = 0.170/–0.163 e Å^{-3}.

CCDC 2429888 and 2526895 contain the supplementary crystallographic information for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

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a R^1 = 4-MeC_6H_4, R^2 = CN, R^3 = pyridin-2-yl
b R^1 = 4-BrC_6H_4, R^2 = CN, R^3 = pyridin-2-yl
c R^1 = R^2 = Ph, R^3 = pyridin-2-yl
d R^1 = R^2 = Ph, R^3 = pyrazin-2-yl
e R^1 = R^2 = Ph, R^3 = pyrimidin-2-yl
f R^1 = 4-MeC_6H_4, R^2 = thiophen-2-yl, R^3 = pyridin-2-yl
g R^1 = 4-MeC_6H_4, R^2 = furan-2-yl, R^3 = pyridin-2-yl
h R^1 = 4-ClC_6H_4, R^2 = 1-methylpyrrol-2-yl, R^3 = pyridin-2-yl

Scheme 1 *Reagents and conditions*: i, *o*-xylene, 150 °C, 8 h (for all **1a**–**h**); ii, DMF, 150 °C, 8 h (additional runs for **1c**,**h**).

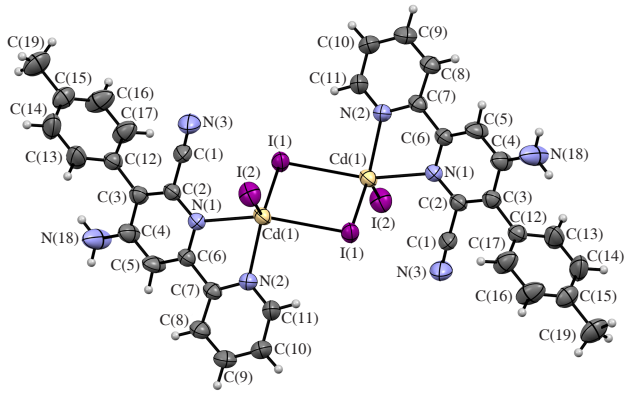
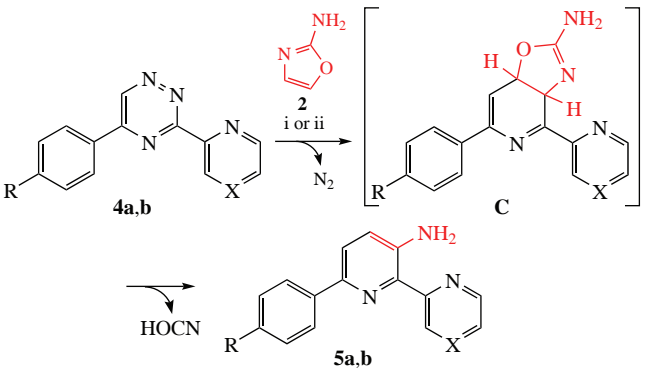


Figure 1 Solid-state structure of a dimeric complex (**3a**·CdI_2)$_2$·2 MeCN (p = 50%, atoms of co-crystallized, MeCN solvate molecules are not shown).

selectivity, involving preferential bonding of the C^4 and C^5 atoms of the oxazole moiety to the C^3 and C^6 positions of the 1,2,4-triazine ring, respectively. Earlier, we showed that this type of addition was characteristic of reactions of 6-unsubstituted 1,2,4-triazines with 4-aryl-2-aminooxazoles.[13] In the reaction



a R = Cl, X = CH, 22% (i), 64% (ii)
b R = H, X = N, 17% (i), 54% (ii)

Scheme 2 *Reagents and conditions*: i, *o*-xylene, 150 °C, 8 h; ii, DMF, 150 °C, 8 h.

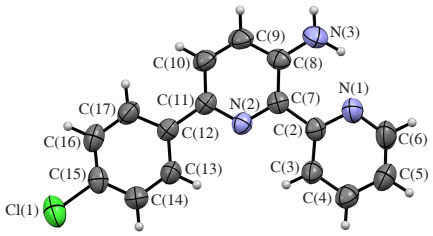


Figure 2 General view of the molecule **5a** in crystal in thermal ellipsoid representation (p = 50%).

of 6-unsubstituted 1,2,4-triazines **4a**,**b** with 2-aminooxazole, 6-aryl-2-hetaryl-3-aminopyridines **5a**,**b** were obtained (Scheme 2). The structure of compound **5a** was confirmed, along with other methods, by X-ray diffraction analysis (Figure 2).†

Notably, the reaction efficiency was significantly improved when DMF was used instead of *o*-xylene in the case of 6-unsubstituted 1,2,4-triazines **4a**,**b** (see Scheme 2). Attempts to perform the reaction of other substituted triazines (**1c**,**h**, see Scheme 1) under similar conditions did not lead to improvement in the yields. In contrast to our previous studies on 2-amino-4-aryloxazoles and 1,2,4-triazines, where solvent-free conditions proved effective,[11–13] attempts to carry out the reaction of unsubstituted 2-aminooxazole **2** with 1,2,4-triazines under solvent-free conditions resulted in strong decomposition of the amine accompanied by partial sublimation, while only traces of the desired products were observed.

The photophysical properties of the synthesized 4-aminopyridines **3a**–**h** and 3-aminopyridines **5a**,**b** were investigated by UV–VIS absorption and fluorescence spectroscopy in acetonitrile solutions. The compounds exhibit absorption maxima in the 220–370 nm range and emit in the blue region (392–464 nm). In contrast to the 4-aminopyridines **3**, the 3-aminopyridines **5** display an additional long-wavelength absorption band (328–370 nm), which may be associated with an intramolecular N–H···N hydrogen bonding interaction between the amino group and the nitrogen atom of the azine ring. The fluorescence quantum yields vary considerably depending on the substitution pattern (<0.1–57.2%). The absorption and emission spectra (Figures S5–S7) together with the corresponding photophysical parameters (Table S1) are provided in Online Supplementary Materials.

In conclusion, an alternative ring-opening pathway of oxazole-derived cycloadducts was identified in the IEDDA reactions of 1,2,4-triazines with 2-aminooxazoles. Although a related ring-opening process has previously been reported for the reaction of 1,2,4,5-tetrazines with oxazole,[15] the present transformation results in the formation of amino-substituted pyridines rather than the corresponding ring-opened formamide derivatives. The substitution pattern of the triazine core governs the reaction outcome, enabling the selective formation of either 4- or 3-aminopyridines. The photophysical properties of the synthesized aminopyridines were also explored, revealing blue fluorescence with substituent-dependent emission efficiencies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8112.

References

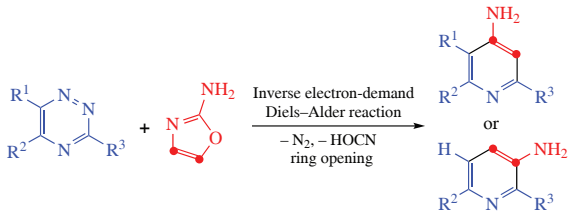
1 F.-G. Zhang, Z. Chen, X. Tang and J.-A. Ma, *Chem. Rev.*, 2021, **121**, 14555; https://doi.org/10.1021/acs.chemrev.1c00611.
2 D. L. Boger, *Tetrahedron*, 1983, **39**, 2869; https://doi.org/10.1016/S0040-4020(01)92154-4.
3 D. L. Boger and J. S. Panek, *J. Org. Chem.*, 1981, **46**, 2179; https://doi.org/10.1021/jo00323a044.
4 K. Müller and J. Sauer, *Tetrahedron Lett.*, 1984, **25**, 2541; https://doi.org/10.1016/S0040-4039(01)81226-0.
5 S. P. Stanforth, B. Tarbit and M. D. Watson, *Tetrahedron Lett.*, 2002, **43**, 6015; https://doi.org/10.1016/S0040-4039(02)01215-7.
6 S. P. Stanforth, B. Tarbit and M. D. Watson, *Tetrahedron*, 2004, **60**, 8893; https://doi.org/10.1016/j.tet.2004.07.024.
7 S.-W. Wang, W.-S. Guo, L.-R. Wen and M. Li, *RSC Adv.*, 2014, **4**, 59218; https://doi.org/10.1039/C4RA11294F.
8 B. R. Lahue, Z.-K. Wan and J. K. Snyder, *J. Org. Chem.*, 2003, **68**, 4345; https://doi.org/10.1021/jo030049y.
9 S. C. Benson, J. H. Li and J. K. Snyder, *J. Org. Chem.*, 1992, **57**, 5285; https://doi.org/10.1021/jo00046a005.
10 J. H. Li and J. K. Snyder, *J. Org. Chem.*, 1993, **58**, 516; https://doi.org/10.1021/jo00054a044.
11 A. P. Krinochkin, G. M. Reddy, D. S. Kopchuk, P. A. Slepukhin, Ya. K. Shtaitz, I. A. Khalymbadzha, I. S. Kovalev, G. A. Kim, I. N. Ganebnykh, G. V. Zyryanov, O. N. Chupakhin and V. N. Charushin, *Mendeleev Commun.*, 2021, **31**, 542; https://doi.org/10.1016/j.mencom.2021.07.035.
12 A. Rammohan, Ya. K. Shtaitz, E. D. Ladin, A. P. Krinochkn, P. A. Slepukhin, V. V. Sharutin, E. R. Sharafieva, T. A. Pospelova, D. S. Kopchuk and G. V. Zyryanov, *Russ. J. Gen. Chem.*, 2023, **93**, 263; https://doi.org/10.1134/S1070363223020056.
13 Y. K. Shtaitz, A. Rammohan, A. P. Krinochkin, E. D. Ladin, I. I. Butorin, N. N. Mochulskaya, I. A. Khalymbadzha, P. A. Slepukhin, V. A. Shevyrin, D. S. Kopchuk, G. V. Zyryanov and O. N. Chupakhin, *ChemistrySelect*, 2023, **8**, e202300903; https://doi.org/10.1002/slct.202300903.
14 J. Shao, W. Yu, Z. Shao and Y. Yu, *Chem. Commun.*, 2012, **48**, 2785; https://doi.org/10.1039/c2cc17850h.
15 G. Seitz, R. Hoferichter and R. Mohr, *Arch. Pharm.*, 1989, **322**, 415; https://doi.org/10.1002/ardp.19893220707.

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Contents entry

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