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Synthesis of 2-amino-3,6-di(het)arylpyridines from 5-cyano-3,6-di(het)aryl-1,2,4-triazines and arylhydrazines *via* the S_N^{ipso}/*aza*-Diels–Alder reaction sequence

Alexey P. Krinochkin,[a,b] Mallikarjuna R. Guda,[a] Aluru Rammohan,[a] Dmitry S. Kopchuk,[a,b] Igor L. Nikonov,*[a,b] Evgeny D. Ladin,[a] Sougata Santra,[a] Ilya N. Egorov,[a] Grigory V. Zyryanov[a,b] and Oleg N. Chupakhin[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: +7 343 375 4501; e-mail: igor.nikonov.ekb@gmail.com*

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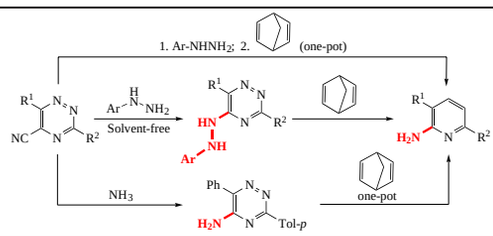
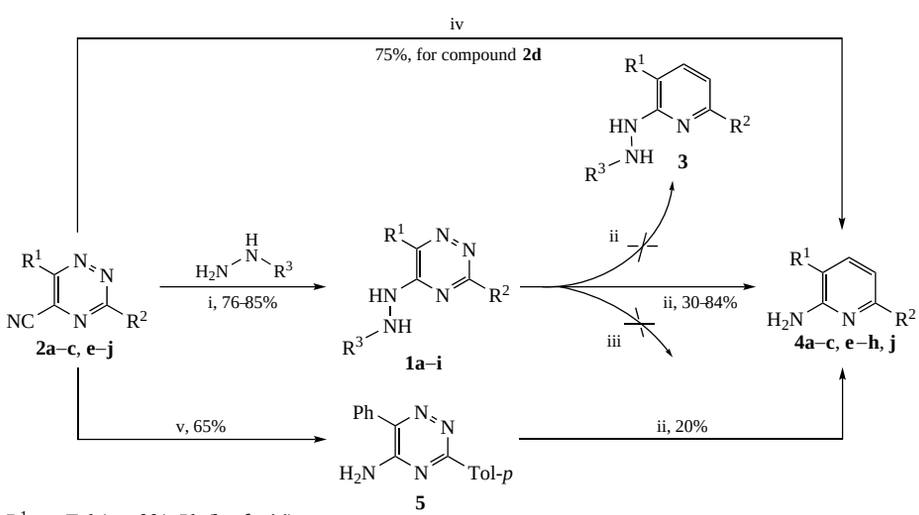
Reaction between 5-cyano-3,6-di(het)aryl-1,2,4-triazines and arylhydrazines with the following *aza*-Diels–Alder autoclave reaction affords hardly available 2-amino-3,6-di(het)aryl-pyridines in up to 67% yield after two steps and in 75% yield for the one-pot way. The compounds obtained can be promising for medicinal chemistry.



Keywords: 2-aminopyridines, 6-amino-2,2′-bipyridines, 1,2,4-triazines, arylhydrazines, *ipso*-substitution, *aza*-Diels–Alder reaction, autoclave processes.

One of the promising accesses to functionalized (bi)pyridines is the *aza*-Diels–Alder reaction of 1,2,4-triazine precursors bearing nucleophile residues obtained, in turn, by means of S_N^{ipso}/S_N^H reactions.[1–7] This approach is the convenient way for obtaining practically useful pyridines used in engineering, agriculture, medicine, and as pharmaceuticals.[8] For example, (bi)pyridines, as well as their metal complexes, demonstrate promising photophysical[9–13] and liquid crystal properties[14] as well as biological activity.[15–19] They can be used as herbicides, insecticides[20,21] and fluorescent labels.[22,23]

In a number of cases, in addition to the expected transformation of the 1,2,4-triazine ring into a pyridine one under the action of dienophiles, parallel or competitive processes involving some fragments were reported. The reduction of the nitro group into amino one,[24,25] transformation of trichloromethyl into dichloromethyl group,[26,27] partial demethylation of the 8-positioned methoxy group at the quinoline fragment[28] and partial decyanation of C^5-cyano group in 1,2,4-triazine cycle[29] were described. Besides, parallel S_N^H reaction with direct introduction of the pyrrolidine residue[30] and isomerization of



R^1 = *p*-Tol (**a**,**c**,**d**,**h**), Ph (**b**,**e**,**f**,**g**,**i**,**j**)
R^2 = 2-pyridyl (**a**,**b**), *p*-Tol (**c**,**d**,**j**), 2-furyl (**e**), 2-thienyl (**f**), Me (**g**), 2,4-$F_2C_6H_3$ (**h**), Ph (**i**)
R^3 = Ph (**a**,**b**,**d**,**h**), 4-FC_6H_4 (**c**,**e**,**g**), *p*-Tol (**f**), benzothiazol-2-yl (**i**)

Scheme 1 *Reagents and conditions*: i, neat, 150 °C, 8 h, Ar; ii, 2,5-norbornadiene, *o*-dichlorobenzene, pressure vessel, 215 °C, 10 h, Ar; iii, *o*-dichlorobenzene, 180 °C, 36 h, Ar; iv, $PhNHNH_2$, neat, 150 °C, 8 h, then *o*-dichlorobenzene, pressure vessel, 2,5-norbornadiene, 215 °C, 10 h, Ar; v, NH_3 bubbling, DMF, room temperature, 30 min.

furoxanylpyridine derivative with partial migration of the *N*-oxide fragment[31] were demonstrated. The competitive domino-transformation of 3-(2-pyridyl)-1,2,4-triazines under the action of arynes leading to triazolopyridoindoles was studied in details.[32–35] Thus, the further study of the *aza*-Diels–Alder reaction of 1,2,4-triazines on the action of dienophiles looks promising. In this work, we report the results of exploring the transformations of C^5-(het)arylhydrazinyl-substituted 1,2,4-triazines obtained by the reaction of 5-cyano-1,2,4-triazines with (het)arylhydrazines during the *aza*-Diels–Alder reaction with 2,5-norbornadiene.

The starting 3,6-di(het)aryl-substituted 5-[2-(het)arylhydrazinyl]-1,2,4-triazines **1** were synthesized as described[36] by the solvent-free nucleophilic *ipso*-substitution of the C^5-cyano group in 1,2,4-triazines **2** (Scheme 1). Our attempted *aza*-Diels–Alder reaction of 1,2,4-triazine **1a** with 2,5-norbornadiene under common conditions, namely, in refluxing (up to 36 h) *o*-dichlorobenzene brought about the starting compound **1a**. We reported earlier that application of the autoclave conditions for the *aza*-Diels–Alder reaction was effective for the cases where the reaction did not proceed under milder conditions,[6,37,38] and in some cases the shorter reaction times and higher product yields were observed.[39,40]

In fact, the reaction of 1,2,4-triazines **1** with 2,5-norbornadiene in an autoclave in *o*-dichlorobenzene at 215 °C for 10 h, instead of the expected 2-hydrazinylpyridines **3**, gave products **4** (see Scheme 1) with the yield up to 84%. However, their analytical data corresponded to neither expected products **3** nor starting 1,2,4-triazines **1**. In particular, no signals for the arylhydrazide residue were observed in their ^{1}H NMR spectra while new two-proton broad singlets at 4.59–4.73 ppm appeared. The data of ^{13}C NMR, mass-spectrometry and elemental analysis obtained revealed the structure of products **4** as di(het)arylpyridin-2-amines **4**. It is necessary to note that in the case of 1,2,4-triazine **1i** bearing benzothiazole residue in a hydrazine moiety, no product was obtained due to extensive tarring of the reaction mixture. The presence of 2-pyridyl residue at the C^3 position of 1,2,4-triazine does not affect the reaction, and 6-amino-2,2′-bipyridine derivatives **4a**,**b** were successfully obtained.

We did not find direct literature analogies for the preparation of aminopyridines as herein presented. In a number of sources,[41–44] the transformation of 1-substituted 2-phenylhydrazines with the elimination of aniline molecule took place. The fact that the *aza*-Diels–Alder reaction proceeded, regardless of the cleavage of the hydrazine residue, was confirmed by the special experiment. The similar reaction of 5-amino-1,2,4-triazine **5** (obtained from the corresponding 5-cyano-1,2,4-triazine **2j**[45]) with 2,5-norbornadiene led to pyridin-2-amine **4j** in only 20% yield, which is significantly inferior to the use of 2-arylhydrazinyl analogues **1**.

We also demonstrated that the reaction sequence can be performed in one pot. For this, compound **2d** was first reacted with phenylhydrazine (neat, 8 h, autoclave), the reaction mixture was then diluted with *o*-dichlorobenzene, 2,5-norbornadiene was added, and the mixture was autoclaved (215 °C, 10 h) to afford product **4c** in 75% yield, which is a little higher compared to two-step sequence.

2-Aminopyridines successfully prepared in this work can be of interest for the synthesis of various biologically active substances, *e.g.*, imidazo[1,2-*a*]pyridines demonstrating wide spectrum of biological activity.[46] A number of drugs contain the substanses of this class. In addition, 2-aminopyridine derivatives exhibited promising biological activities ant they are used as glucokinase activators or selective inhibitors of neuronal nitric oxide synthase.[47,48]

In summary, we have discovered a new parallel transformation of 5-positioned arylhydrazine residues in the 1,2,4-triazines upon *aza*-Diels–Alder reaction with 2,5-norbornadiene. This reaction leads to pharmaceutically valuable 3,6-di(het)aryl-substituted 2-aminopyridines, including 2,2′-bipyridines, in up to 67% yield in a two-step procedure and up to 75% yield in a one-pot method.

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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.2022.11.006.

References

1 O. C. Pfüller and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8821.
2 V. N. Kozhevnikov, D. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, M. Zabel and B. König, *J. Org. Chem.*, 2003, **68**, 2882.
3 M. I. Savchuk, A. P. Krinochkin, A. Rammohan, A. F. Khasanov, D. S. Kopchuk, I. N. Egorov, S. Santra, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Mendeleev Commun.*, 2020, **30**, 610.
4 S.-W. Wang, W.-S. Guo, Li-R. Wen and M. Li, *RSC Adv.*, 2014, **4**, 59218.
5 N. Catozzi, W. J. Bromley, P. Wasnaire, M. Gibson and R. J. K. Taylor, *Synlett*, 2007, **14**, 2217.
6 M. I. Savchuk, Ya. K. Shtaitz, D. S. Kopchuk, G. V. Zyryanov, O. S. Eltsov, T. A. Pospelova, V. L. Rusinov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2019, **55**, 985.
7 S. P. J. T. Bachollet, D. Volz, B. Fiser, S. Münch, F. Rönicke, J. Carrillo, H. Adams, U. Schepers, E. Gomez-Bengoa, S. Bräse and J. P. A. Harrity, *Chem. – Eur. J.*, 2016, **22**, 12430.
8 A. M. Prokhorov and D. N. Kozhevnikov, *Chem. Heterocycl. Compd.*, 2012, **48**, 1153 (*Khim. Geterotsikl. Soedin.*, 2012, **48**, 1237).
9 E. Birckner, U.-W. Grummt, A. H. Göller, T. Pautzsch, D. A. M. Egbe, M. Al-Higari and E. Klemm, *J. Phys. Chem. A*, 2001, **105**, 10307.
10 A. Harriman, M. Hissler and R. Ziessel, *Phys. Chem. Chem. Phys.*, 1999, **1**, 4203.
11 J. Vicente, J. Gil-Rubio, N. Barquero, P. G. Jones and D. Bautista, *Organometallics*, 2008, **27**, 646.
12 N. Mizuyama, Y. Tominaga, S. Kohra, K. Ueda, S. Hirayama and Y. Shigemitsu, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 602.
13 M. Sellstedt, A. Nyberg, E. Rosenbaum, P. Engström, M. Wickström, J. Gullbo, S. Bergström, L. B.-Å. Johansson and F. Almqvist, *Eur. J. Org. Chem.*, 2010, **32**, 6171.
14 F. Camerel, G. Ulrich and R. Ziessel, *Org. Lett.*, 2004, **6**, 4171.
15 B. H. Lange and T. W. Schwartz, *Patent WO 2003055477 A1*, 2003.
16 Y. Teshima, K. Shin-ya, A. Shimazu, K. Furihata, H. S. Chul, K. Furihata, Y. Hayakawa, K. Nagai and H. Seto, *J. Antibiot.*, 1991, **44**, 685.
17 D. L. Boger and J. S. Panek, *J. Org. Chem.*, 1981, **46**, 2179.
18 M. Niewerth, D. Kunze, M. Seibold, M. Schaller, H. C. Korting and B. Hube, *Antimicrob. Agents Chemother.*, 2003, **47**, 1805.
19 G. Koster, H. J. Bekema, J. Wetterslev, C. Gluud, F. Keus and I. C. C. van der Horst, *Intensive Care Med.*, 2016, **42**, 1322.
20 M. R. TePaske, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *Tetrahedron Lett.*, 1991, **32**, 5687.
21 K. Morimoto, H. Furusawa, T. Terachi, T. Nawamaki, S. Watanabe, K. Nakahira and J. Noguchi, *Patent WO 9857957*, 1999.
22 M. Hagimori, N. Mizuyama, Y. Tominaga, T. Mukai and H. Saji, *Dyes Pigm.*, 2015, **113**, 205.
23 G. V. Zyryanov, D. S. Kopchuk, I. S. Kovalev, S. Santra, M. Rahman, A. F. Khasanov, A. P. Krinochkin, O. S. Taniya, O. N. Chupakhin and V. N. Charushin, *Mendeleev Commun.*, 2020, **30**, 537.
24 D. S. Kopchuk, A. F. Khasanov, I. S. Kovalev, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Mendeleev Commun.*, 2013, **23**, 209.
25 M. Lorion, G. Guillaumet, J.-F. Brière and F. Suzenet, *Org. Lett.*, 2015, **17**, 3154.
26 N. V. Chepchugov, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Mendeleev Commun.*, 2016, **26**, 220.

27 D. S. Kopchuk, A. P. Krinochkin, I. S. Kovalev, O. S. Taniya, G. V. Zyryanov, V. L. Rusinov, O. N. Chupakhin, A. Yu. Petrov and A. I. Suvorova, *AIP Conf. Proc*., 2020, **2280**, 040024.
28 M. I. Savchuk, D. S. Kopchuk, I. N. Egorov, A. F. Khasanov, S. S. Rybakova, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Russ. J. Gen. Chem*., 2021, **91**, 779 (*Zh. Obshch. Khim*., 2021, **91**, 688).
29 D. S. Kopchuk, A. F. Khasanov, N. V. Chepchugov, I. S. Kovalev, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Russ. J. Org. Chem*., 2017, **53**, 99.
30 Y. F. Sainz, S. A. Raw and R. J. K. Taylor, *J. Org. Chem*., 2005, **70**, 10086.
31 L. L. Fershtat, A. A. Larin, M. A. Epishina, I. V. Ovchinnikov, A. S. Kulikov, I. V. Ananyev and N. N. Makhova, *RSC Adv*., 2016, **6**, 31526.
32 I. L. Nikonov, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. F. Khasanov, P. A. Slepukhin, V. L. Rusinov and O. N. Chupakhin, *Tetrahedron Lett*., 2013, **54**, 6427.
33 D. S. Kopchuk, I. L. Nikonov, G. V. Zyryanov, I. S. Kovalev, V. L. Rusinov and O. N. Chupakhin, *Chem. Heterocycl. Compd*., 2014, **50**, 907 (*Khim. Geterotsikl. Soedin*., 2014, **50**, 983).
34 D. S. Kopchuk, N. V. Chepchugov, O. S. Taniya, A. F. Khasanov, K. Giri, I. S. Kovalev, S. Santra, G. V. Zyryanov, A. Majee, V. L. Rusinov and O. N. Chupakhin, *Tetrahedron Lett*., 2016, **57**, 5639.
35 D. S. Kopchuk, I. L. Nikonov, A. F. Khasanov, K. Giri, S. Santra, I. S. Kovalev, E. V. Nosova, S. Gundala, P. Verkatapuram, G. V. Zyryanov, A. Majee and O. N. Chupakhin, *Org. Biomol. Chem*., 2018, **16**, 5119.
36 A. P. Krinochkin, M. R. Guda, A. Rammohan, D. S. Kopchuk, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Chim. Techno Acta*, 2020, **7**, 204.
37 Ya. K. Shtaitz, M. I. Savchuk, E. S. Starnovskaya, A. P. Krinochkin, D. S. Kopchuk, S. Santra, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *AIP Conf. Proc*., 2019, **2063**, 040050.
38 M. I. Savchuk, E. S. Starnovskaya, Ya. K. Shtaitz, D. S. Kopchuk, E. V. Nosova, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Russ. J. Gen. Chem*., 2018, **88**, 2213 (*Zh. Obshch. Khim*., 2018, **88**, 1728).
39 M. M. Krayushkin, I. P. Sedishev, V. N. Yarovenko, I. V. Zavarzin, S. K. Kotovskaya, D. N. Kozhevnikov and V. N. Charushin, *Russ. J. Org. Chem*., 2008, **44**, 407 (*Zh. Org. Khim*., 2008, **44**, 411).
40 M. Z. Shafikov, D. N. Kozhevnikov, M. Bodensteiner, F. Brandl and R. Czerwieniec, *Inorg. Chem*., 2016, **55**, 7457.
41 F. Alonso, P. Candela, C. Gomez and M. Yus, *Adv. Synth. Catal*., 2003, **345**, 275.
42 Y. Zhang, Q. Tang and M. Luo, *Org. Biomol. Chem*., 2011, **9**, 4977.
43 F. Ren, Y. Zhang, L. Hu and M. Luo, *Arkivoc*, 2013, (**iii**), 165.
44 B. Zhou, J. Song, H. Zhou, T. Wu and B. Han, *Chem. Sci*., 2016, **7**, 463.
45 D. N. Kozhevnikov, V. N. Kozhevnikov, I. S. Kovalev, V. L. Rusinov, O. N. Chupakhin and G. G. Aleksandrov, *Russ. J. Org. Chem*., 2002, **38**, 744 (*Zh. Org. Khim*., 2002, **38**, 780).
46 R. N. Rao and K. Chanda, *Chem. Commun*., 2022, **58**, 343.
47 K. J. Orie, R. U. Duru and R. I. Ngochindo, *Am. J. Heterocycl. Chem*., 2021, **7**, 11.
48 M. Marinescu, *Int. J. Pharm. Biol. Sci*., 2017, **8**, 338.

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