ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 7, pp. 963–970. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © A.P. Krinochkin, D.S. Kopchuk, N.V. Chepchugov, I.S. Kovalev, G.V. Zyryanov, V.L. Rusinov, O.N. Chupakhin, 2017, published in Zhurnal Organicheskoi Khimii, 2017, Vol. 53, No. 7, pp. 951–958.

Effect of Substituent in Pyridine-2-carbaldehydes on Their Heterocyclization to 1,2,4-Triazines and 1,2,4-Triazine 4-Oxides

A. P. Krinochkin[a], D. S. Kopchuk[a, b], N. V. Chepchugov[a], I. S. Kovalev[a], G. V. Zyryanov[a, b],* V. L. Rusinov[a, b], and O. N. Chupakhin[a, b]

[a] *Yeltsin Ural Federal University, ul. Mira 19, Yekaterinburg, 620002 Russia*
**e-mail: gvzyryanov@gmail.com*

[b] *Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, ul. S. Kovalevskoi/Akademicheskaya 22/20, Yekaterinburg, 620990 Russia*

Received October 26, 2016

Abstract—A series of substituted pyridine-2-carbaldehydes were brought into heterocyclization with isonitrosoacetophenone hydrazones, followed by aromatization by the action of oxidants or by dehydration in boiling acetic acid. As a result, substituted 3-(pyridin-2-yl)-1,2,4-triazines or 3-(pyridin-2-yl)-1,2,4-triazine 4-oxides were formed. 6-Formylpyridine-2-carbonitrile failed to undergo heterocyclization, 6-methylpyridine-2-carbaldehyde and methyl 6-formylpyridine-3-carboxylate can be converted to both 1,2,4-triazine and 1,2,4-triazine 4-oxide derivative, and only 1,2,4-triazine 4 oxides were obtained from 6-bromopyridine-2-carbaldehyde and 6-formyl-3-phenylpyridine-2-carbonitrile. Convenient procedures were proposed for the synthesis of some initial pyridinecarbaldehydes.

DOI: 10.1134/S1070428017070016

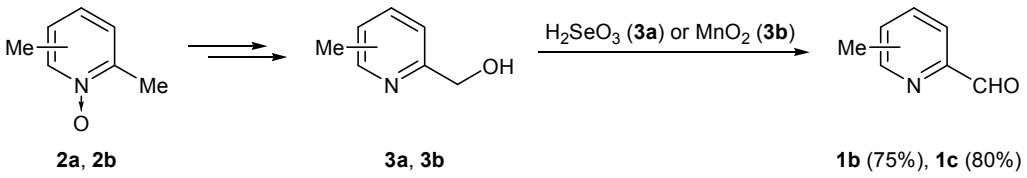
3-(Pyridin-2-yl)-1,2,4-triazines and their fused derivatives constitute an important class of heterocyclic compounds which offer a wide potential for use in practice for various purposes. In particular, 3-(pyridin-2-yl)-1,2,4-triazines are intermediate products in the synthesis of bipyridines [1–3] (including cycloalkene-fused derivatives [4–6]), 1-(pyridin-2-yl)isoquinolines [7], (pyridin-2-yl)azatriphenylenes [8], and 10-(1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles [9–11] via recently discovered rearrangement with aryne intermediates. 1,2,4-Triazines can be successfully functionalized by nucleophilic substitution of hydrogen (S_N^H), and successive S_N^H and aza-Diels–Alder reactions give rise to 2,2′-bipyridines with a variety of substituents (e.g., carborane and acetylene residues, etc.), which are difficult to obtain by other methods [12–14]. 3-(Pyridin-2-yl)-1,2,4-triazines can be used as reagents for spectrophotometric determination of metal cations [15], gene expression promoters [16], and selective extractants for lanthanides and actinides [17].

3-(Pyridin-2-yl)-1,2,4-triazines are generally synthesized by condensation of isonitrosoacetophenone hydrazones with pyridine-2-carbaldehydes. This reaction can involve both oxidative aromatization of intermediate product with formation of 1,2,4-triazine 4-oxides [18] and its dehydration in boiling acetic acid to produce just 3-(pyridin-2-yl)-1,2,4-triazines [1]. Following this approach, heterocyclizations of pyridine-2-carbaldehyde and its 6-methyl [19], 6-hydroxymethyl [20], and 5- [1] and 6-methoxycarbonyl derivatives [19, 21] have been reported, though the potential of functionalization of pyridine-2-carbaldehyde is much wider.

In this work we studied the behavior of 3-methyl-, 6-methyl-, and 6-bromopyridine-2-carbaldehydes, methyl 6-formylpyridine-3-carboxylate, 6-formylpyridine-2-carbonitrile, and 6-formyl-3-phenylpyridine-2-carbonitrile in analogous heterocyclizations with the goal of obtaining 3-(pyridin-2-yl)-1,2,4-triazines or 3-(pyridin-2-yl)-1,2,4-triazine 4-oxides. 6-Bromopyridine-2-carbaldehyde (**1a**) is a commercially available reagent, while the other aldehydes were prepared from readily accessible initial compounds according to procedures optimized by us.

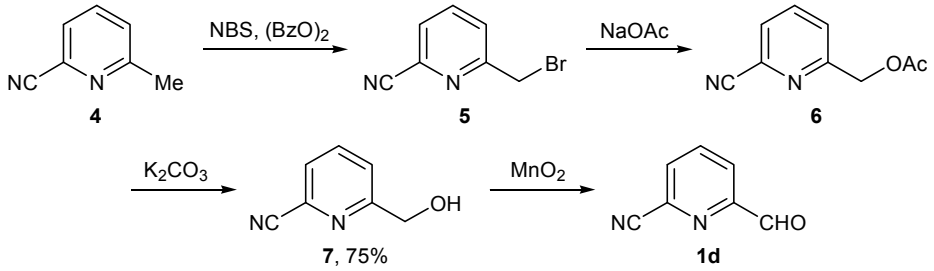
3- and 6-Methylpyridine-2-carbaldehydes **1b** and **1c** were previously synthesized from 2,3-dimethylpyridine [22] and 2,6-dimethylpyridine [23], respectively (Scheme 1). *N*-Oxides **2a** and **2b** were treated

Scheme 1.



1b, **2a**, **3a**, 6-Me; **1c**, **2b**, **3b**, 3-Me.

Scheme 2.



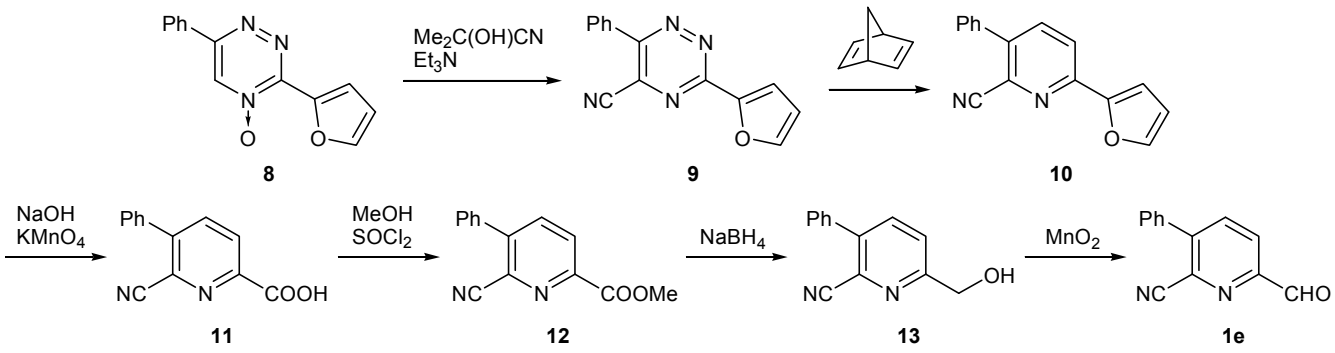
with acetic anhydride, and subsequent hydrolysis of the resulting (pyridin-2-yl)methyl acetates gave 3- and 6-methylpyridin-2-ylmethanols **3a** and **3b** which were oxidized to aldehydes **1b** and **1c**, respectively. 6-Methylpyridine-2-carbaldehyde (**1b**) was also prepared according to a simplified procedure (compared to [23]) with the use of selenous acid. It was found that the reaction with selenium dioxide is accompanied by partial oxidation of the α-methyl group. 3-Methylpyridine-2-carbaldehyde (**1c**) cannot be obtained by oxidation of **3b** with selenous acid or selenium dioxide; therefore, aldehyde **1c** was synthesized according to simplified procedure [24] using activated manganese dioxide as oxidant.

6-Formylpyridine-2-carbonitrile (**1d**) was prepared from 6-methylpyridine-2-carbonitrile (**4**) [25] (Scheme 2). Radical bromination of **4** with *N*-bromosuccinimide (according to optimized procedure [25]), followed by nucleophilic substitution of bromine by acetoxy group, alkaline hydrolysis, and oxidation afforded aldehyde **1d**. 6-Formyl-3-phenylpyridine-2-carbonitrile (**1e**) was synthesized as shown in Scheme 3, starting from 3-(furan-2-yl)-6-phenyl-1,2,4-triazine 4-oxide (**8**) [26]. Nucleophilic substitution of hydrogen in the triazine ring of **8** by cyano group [27], transformation of the 1,2,4-triazine ring to pyridine by the aza-Diels–Alder reaction [18], oxidation of the furyl substituent to carboxy group, and subsequent esterification, reduction of the ester group to hydroxymethyl, and oxidation afforded aldehyde **1e**.

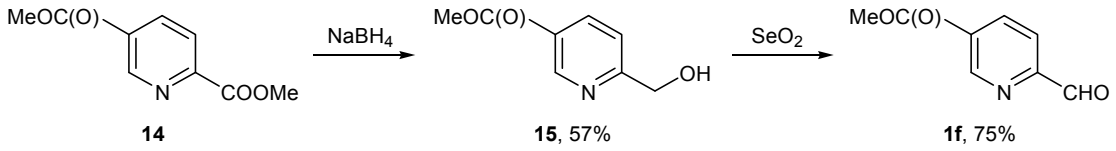
Methyl 6-formylpyridine-3-carboxylate **1f** was obtained according to the procedure described previously [1] from dimethyl pyridine-2,5-dicarboxylate (**14**) via selective reduction of the ester group in the 2-position and subsequent oxidation of alcohol **15** with selenium dioxide (Scheme 4).

Aldehydes **1a**–**1f** were brought into heterocyclization with isonitrosoacetophenone hydrazones (Scheme 5; for R^1, R^2, R^3, see table). As we showed previously, aldehydes **1b** and **1f** can be converted to

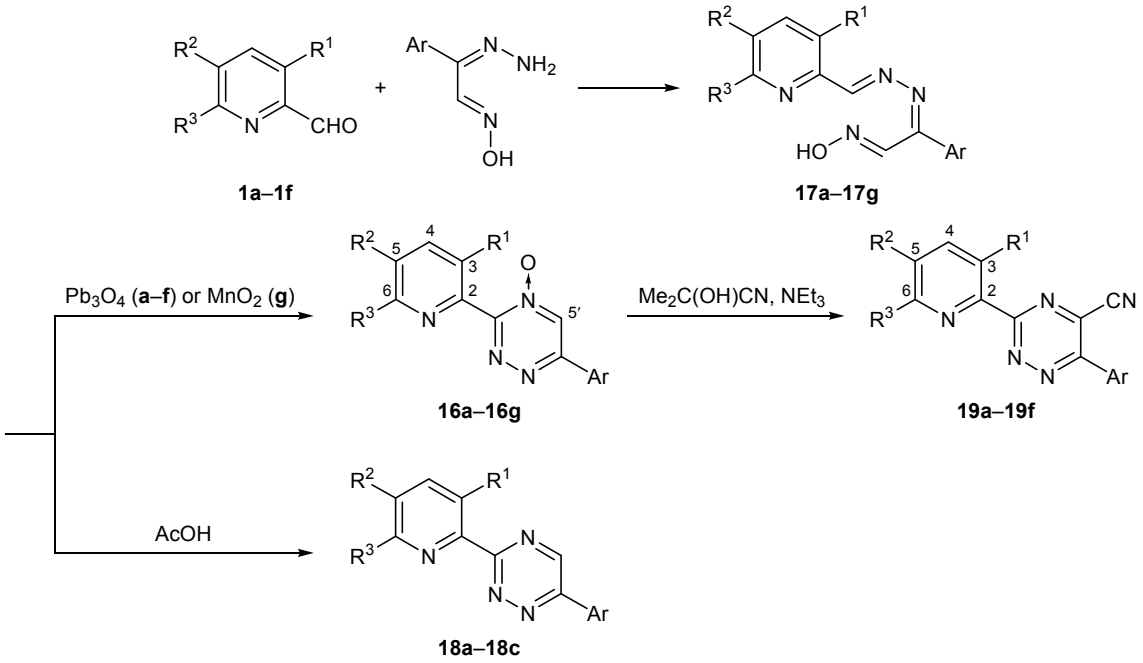
Scheme 3.



Scheme 4.



Scheme 5.



the corresponding 1,2,4-triazines in up to 62 [19] and 55% yield [1], respectively. In this work we found that the same aldehydes can also be used to synthesize triazine 4-oxides **16**. 1,2,4-Triazine 4-oxides **16b** and **16c** were readily obtained from 6-methylpyridine-2-carbaldehyde (**1b**) according to the procedure described in [18] by oxidative aromatization of intermediates **17b** and **17c** with red lead oxide (Pb_3O_4). The oxidation under the same conditions of intermediate **17g** derived from methyl 6-formylpyridine-3-carboxylate (**1f**) gave no 1,2,4-triazine 4-oxide **16g**, so that the procedure needed to be modified. By using activated manganese dioxide as oxidant we succeeded in obtaining 1,2,4-triazine 4-oxide **16g** in 52% yield.

The reactions with the other pyridine-2-carbaldehydes revealed some essential limitations. Neither 1,2,4-triazine **18** nor 4-oxide **16** was obtained from compound **1d** regardless of the conditions, and a com-

Heterocyclization of pyridine-2-carbaldehydes **1a**–**1f**

Initial aldehyde (**1**), intermediate (**17**)	R^1	R^2	R^3	Ar	Yield, %		
					18	**16**	**19**
1a, **17a**	H	H	Br	Ph	–	**16a**, 57	**19a**, 83
1b, **17b**	H	H	Me	Ph	**18a**, 50 [18]	**16b**, 40	**19b**, 70
1b, **17c**	H	H	Me	4-$MeOC_6H_4$	**18b**, 62 [18]	**16c**, 35	**19c**, 76
1c, **17d**	Me	H	H	Ph	–	**16d**, 50	**19d**, 50
1d, –	H	H	CN	Ph	–	–	–
1e, **17e**	H	Ph	CN	Ph	–	**16e**, 64	
1e, **17f**	H	Ph	CN	4-MeC_6H_4	–	**16f**, 60	**19e**, 73
1f, **17g**	H	COOMe	H	Ph	**18c**, 48 [1]	**16g**, 52	**19f**, 65

plex mixture of unidentified products was formed, presumably due to side reactions involving the cyano group. Introduction of an additional phenyl substituent (compound **1e**) is likely to induce electron density redistribution in the pyridine ring and/or shielding of the cyano group, so that the latter becomes considerably less reactive. As a result, we isolated 1,2,4-triazine 4-oxides **16e** and **16f**, but the corresponding intermediates **17e** and **17f** did not undergo dehydration to 1,2,4-triazines **18**. Likewise, 3-methyl- and 6-bromopyridine-2-carbaldehydes **1a** and **1c** were converted to only 1,2,4-triazine 4-oxides **16a** and **16d**, whereas no 1,2,4-triazines **18** were obtained therefrom.

In the final stage of our study, we examined the possibility of further functionalization of triazine 4-oxides **16** by nucleophilic substitution of hydrogen with acetone cyanohydrin and triethylamine [27]. In all cases, the corresponding 1,2,4-triazine-5-carbonitriles **19** were formed, but the reactions with 6-bromo- and 3-methyl-1,2,4-triazine 4-oxides **16a** and **16d** required more severe conditions to achieve complete conversion (the reactions were carried out in boiling 1,2-dichloroethane under reflux rather than at 50°C, and the reaction time was longer).

In summary, substituted pyridine-2-carbaldehydes react with isonitrosoacetophenone hydrazones to give the corresponding 1,2,4-triazine 4-oxides or 1,2,4-triazines as a result of oxidative aromatization or thermal dehydration (in boiling acetic acid). 1,2,4-Triazine 4-oxides were formed in most cases, regardless of the substituent in the pyridine ring (except for 6-formylpyridine-2-carbonitrile). 3-(Pyridin-2-yl)-1,2,4-triazines were obtained by dehydration in boiling acetic acid only from 6-methylpyridine-2-carbaldehyde and methyl 6-formylpyridine-3-carboxylate. 3-Methyl- and 6-bromopyridine-2-carbaldehydes and 3-phenyl-6-formylpyridine-2-carbonitrile were not converted to corresponding 1,2,4-triazines.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 MHz using tetramethylsilane as internal standard. The melting points were measured on a Boetius melting point apparatus. The mass spectra (electrospray ionization) were obtained on a Bruker Daltonics MicrOTOF-Q II instrument (Bremen, Germany). The elemental compositions were determined with a Perkin Elmer 2400 Series II CHN analyzer.

Initial isonitrosoacetophenone hydrazones [28], 6-methylpyridine-2-carbonitrile (**4**) [25], 3-(furan-2-yl)-6-phenyl-1,2,4-triazine 4-oxide (**8**) [26], methyl 6-formylpyridine-3-carboxylate (**1f**) [1], and 6-(hydroxymethyl)pyridine-2-carbonitrile (**7**) [29] were synthesized according to known methods.

6-Methylpyridine-2-carbaldehyde (1b). A solution of 10.47 g (0.081 mol) of selenous acid in 30 mL of water was added with stirring to a solution of 20 g (0.162 mol) of (6-methylpyridin-2-yl)methanol (**3a**) in 150 mL of 1,4-dioxane, and the mixture was stirred for 6 h at 100°C. Metallic selenium was filtered off, the solvent was distilled off from the filtrate under reduced pressure, and the residue was treated with hot hexane (3×150 mL). The solvent was distilled off from the combined extracts under reduced pressure, and the product was not purified additionally. Yield 14.76 g (0.121 mol, 75%), mp 31–33°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.61 s (3H, Me), 7.49 d (1H, 5-H, J = 7.5 Hz), 7.71 d (1H, 3-H, J = 7.5 Hz), 7.86 d.d (1H, 4-H, J = 7.5, 7.5 Hz), 9.93 s (1H, CHO). Mass spectrum: m/z 122.06 (I_{rel} 100%) $[M + H]^+$. Calculated: M 122.06.

Radical bromination of 6-methylpyridine-2-carbonitrile (4). Compound **4**, 1 g (8.46 mmol), was dissolved in 50 mL of anhydrous carbon tetrachloride, 1.51 g (8.46 mmol) of *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide were added, and the mixture was refluxed for 10 h under irradiation with bright light. The precipitate was filtered off, the filtrate was evaporated under reduced pressure, and the residue was subjected to column chromatography using methylene chloride–ethyl acetate (100 : 1) as eluent to isolate 6-(bromomethyl)pyridine-2-carbonitrile (**5**) and minor 6-(dibromomethyl)pyridine-2-carbonitrile.

6-(Bromomethyl)pyridine-2-carbonitrile (5). Yield 590 mg (2.99 mmol, 35%), mp 79–81°C, R_f 0.45. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.66 s (2H, CH_2Br), 7.82–7.89 m (2H, 3-H, 5-H), 8.03 d.d (1H, 4-H, J = 7.8, 7.8 Hz). Mass spectrum: m/z 196.97 (I_{rel} 100%) $[M + H]^+$. Calculated: M 196.97.

6-(Dibromomethyl)pyridine-2-carbonitrile. Yield 150 mg (0.54 mmol, 6%), mp 114–116°C, R_f 0.75. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.22 s (1H, $CHBr_2$), 7.95 m (1H), 8.10–8.17 m (2H). Mass spectrum: m/z 274.88 (I_{rel} 100%) $[M + H]^+$. Calculated: M 274.88.

(6-Cyanopyridin-2-yl)methyl acetate (6). A mixture of 820 mg (4.16 mmol) of compound **5** and 3.41 g

(41.6 mmol) of sodium acetate was dispersed in 40 mL of anhydrous DMF, and the mixture was stirred for 10 h at 130°C. The solvent was distilled off under reduced pressure, the residue was treated with 10 mL of water and extracted with methylene chloride (3× 20 mL), the combined extracts were evaporated, and the residue was used in the next stage without additional purification. Yield 670 mg (3.79 mmol, 91%), light oily material. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.14 s (3H, Me), 5.17 s (2H, CH_2), 7.70 d and 7.86 d (1H each, 3-H, 5-H, J = 7.7 Hz), 8.03 d.d (1H, 4-H, J = 7.7, 7.7 Hz). Mass spectrum: m/z 177.07 (I_{rel} 100%) $[M + H]^+$. Calculated: M 177.07.

3-(Furan-2-yl)-6-phenyl-1,2,4-triazine-5-carbonitrile (9). 1,2,4-Triazine 4-oxide **8**, 5.5 g (22.99 mmol), was dispersed in 50 mL of 1,2-dichloroethane, 3.19 mL (34.48 mmol) of acetone cyanohydrin and 1.6 mL (11.49 mmol) of triethylamine were added, and the mixture was heated for 30 min at 50°C with stirring. The solvent was distilled off under reduced pressure, and the residue was purified by flash chromatography using chloroform as eluent. Yield 3.3 g (13.29 mmol, 58%), mp 128–130°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.79 d.d (1H, Fu, J = 3.6, 2.0 Hz), 7.62–7.68 m (4H, Ph, Fu), 8.04 m (3H, Ph, Fu). Mass spectrum: m/z 249.08 (I_{rel} 100%) $[M + H]^+$. Calculated: M 249.08.

6-(Furan-2-yl)-3-phenylpyridine-2-carbonitrile (10). 2,5-Norbornadiene, 4.92 mL (48.33 mmol), was added to a suspension of 4 g (16.11 mmol) of compound **9** in 45 mL of *o*-xylene, and the mixture was refluxed for 10 h. An additional 2.46 mL (24.17 mmol) of 2,5-norbornadiene was then added, and the mixture was refluxed for 8 h more. The solvent was distilled off under reduced pressure, and the residue was purified by flash chromatography using chloroform as eluent. An analytical sample was obtained by recrystallization from acetonitrile. Yield 2.78 g (11.28 mmol, 70%), mp 128–130°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.65 d.d (1H, Fu, J = 3.6, 2.0 Hz), 7.25 d (1H, Fu, J = 3.6 Hz), 7.50–7.59 m (3H, Ph), 7.62 m (2H, Ph), 7.79 d (1H, Fu, J = 2.0 Hz), 8.04 d (1H, Py, J = 8.0 Hz), 8.08 d (1H, Py, J = 8.0 Hz). Mass spectrum: m/z 247.09 (I_{rel} 100%) $[M + H]^+$. Found, %: C 77.93; H 4.02; N 11.22. $C_{16}H_{10}N_2O$. Calculated, %: C 78.03; H 4.09; N 11.38. M 247.09.

6-Cyano-5-phenylpyridine-2-carboxylic acid (11). A solution of 0.81 g (20.3 mmol) of sodium hydroxide in 5 mL of water was added to a suspension of 1 g (4.06 mmol) of compound **10** in 17 mL of pyridine. The mixture was stirred for 2 h at room temperature while gradually adding 3.21 g (20.3 mmol) of potassium permanganate. It was then refluxed for 10 min, diluted with 20 mL of water, and heated until it became colorless. The precipitate of manganese dioxide was filtered off and washed with water, the filtrate was evaporated under reduced pressure, 30 mL of water was added to the residue, and the mixture was heated to the boiling point. The undissolved material was filtered off, the filtrate was cooled to room temperature, 5 N aqueous HCl was added to pH 2, and the precipitate was filtered off, washed with water, dried, and used in the next step without additional purification. Yield 600 mg (2.68 mmol, 66%), mp 188–190°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.52–7.63 m (3H, Ph), 7.64–7.70 m (2H, Ph), 8.22 d (1H, Py, J = 7.7 Hz), 8.34 d (1H, Py, J = 7.7 Hz), 13.54 br.s (1H, COOH). Mass spectrum: m/z 223.05 (I_{rel} 100%) $[M - H]^-$. Calculated: M 223.05.

Methyl 6-cyano-5-phenylpyridine-2-carboxylate (12). Thionyl chloride, 1 mL, was added to a suspension of 0.96 g (4.28 mmol) of acid **11** in 25 mL of methanol, and the mixture was refluxed for 20 h. The solvent was distilled off under reduced pressure, and the residue was used in the next step without additional purification. Yield 1.02 g (4.28 mmol, 100%), mp 118–120°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.98 s (3H, OMe), 7.55–7.61 m (3H, Ph), 7.65–7.70 m (2H, Ph), 8.26 d (1H, Py, J = 8.0 Hz), 8.37 d (1H, Py, J = 8.0 Hz). Mass spectrum: m/z 239.08 (I_{rel} 100%) $[M + H]^+$. Calculated: M 239.08.

6-(Hydroxymethyl)-3-phenylpyridine-2-carbonitrile (13). Ester **12**, 700 mg (2.94 mmol), was dispersed in 20 mL of ethanol, 0.56 g (14.7 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at 40°C. An additional portion of $NaBH_4$ (0.28 g, 7.35 mmol) was added, and the mixture was stirred at 40°C for 1 h more. The mixture was diluted with 20 mL of water and extracted with methylene chloride (3×25 mL). The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure, and the residue was used in the next step without additional purification. Yield 400 mg (1.91 mmol, 65%), mp 110–112°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.64 d (2H, C**H**$_2$OH, J = 5.5 Hz), 5.50 t (1H, CH_2O**H**, J = 5.5 Hz), 7.47–7.62 m (5H, Ph), 7.85 d (1H, Py, J = 8.0 Hz), 8.01 d (1H, Py, J = 8.0 Hz). Mass spectrum: m/z 211.09 (I_{rel} 100%) $[M + H]^+$. Calculated: M 211.09.

Aldehydes 1c–1e (*general procedure*). Hydroxymethylpyridine **3b**, **7**, or **13**, 1.9 mmol, was dissolved in 25 mL of 1,2-dichloroethane, 1.65 g (19 mmol) of

activated manganese dioxide was added, and the mixture was stirred for 6 h at 50°C. The precipitate was filtered off, the filtrate was evaporated under reduced pressure, and the residue was used in the next step without additional purification.

3-Methylpyridine-2-carbaldehyde (1c). Yield 185 mg (1.52 mmol, 80%), light oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.66 s (3H, Me), 7.39 d.d (1H, 5-H, J = 7.8, 4.6 Hz), 7.62 d (1H, 4-H, J = 7.8 Hz), 8.66 d (1H, 6-H, J = 4.6 Hz), 10.20 s (1H, CHO). Mass spectrum, m/z 122.06 (I_{rel} 100%) $[M + H]^+$. Calculated: M 122.06.

6-Formylpyridine-2-carbonitrile (1d). Yield 160 mg (1.235 mmol, 65%), mp 80–82°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.06 d.d (1H, 4-H, J = 7.7, 7.7 Hz), 8.16 d.d and 8.36 d.d (1H each, 3-H, 5-H, J = 7.7, 1.0 Hz), 10.20 s (1H, CHO). Mass spectrum: m/z 133.04 (I_{rel} 100%) $[M + H]^+$. Calculated: M 133.04.

6-Formyl-3-phenylpyridine-2-carbonitrile (1e). Yield 240 mg (1.14 mmol, 60%), mp 146–148°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.56–7.63 m (3H, Ph), 7.70 m (2H, Ph), 8.24 d (1H, Py, J = 8.2 Hz), 8.32 d (1H, Py, J = 8.0 Hz), 10.03 s (1H, CHO). Mass spectrum: m/z 209.07 (I_{rel} 100%) $[M + H]^+$. Calculated: M 209.07.

1,2,4-Triazine-4-oxides 16 (*general procedure*). Aldehyde **1a**–**1f**, 1 mmol, was dissolved in 15 mL of ethanol, a solution of 1 mmol of the corresponding isonitrosoacetophenone hydrazone in 25 mL of ethanol was added, and the mixture was stirred for 10 h at room temperature. The solvent was distilled off under reduced pressure, the residue was dispersed in 5 mL of acetic acid, and the mixture was stirred for 1 h on cooling with a water bath while gradually adding 0.685 g (1 mmol) of red lead oxide. The mixture was then stirred for 30 min on cooling and diluted with 50 mL of water with stirring, and the precipitate was filtered off, washed with water, and dried. Analytical samples were obtained by recrystallization from ethanol.

3-(6-Bromopyridin-2-yl)-6-phenyl-1,2,4-triazine 4-oxide (16a). Yield 187 mg (0.57 mmol, 57%), mp 218–220°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.55–7.64 m (3H, Ph), 7.80 d (1H, 5-H, J = 7.9 Hz), 7.96 d.d (1H, 4-H, J = 7.9, 7.9 Hz), 8.14 d (1H, 3-H, J = 7.9 Hz), 8.21–8.27 m (2H, Ph), 9.37 s (1H, 5′-H). Mass spectrum: m/z 329.00 (I_{rel} 100%) $[M + H]^+$. Found, %: C 50.90; H 2.59; N 16.87. $C_{14}H_9BrN_4O$. Calculated, %: C 51.09; H 2.76; N 17.02. M 329.00.

3-(6-Methylpyridin-2-yl)-6-phenyl-1,2,4-triazine 4-oxide (16b). Yield 106 mg (0.4 mmol, 40%), mp 206–208°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.61 s (3H, Me), 7.41 d (1H, 5-H, J = 7.8 Hz), 7.54–7.62 m (3H, Ph), 7.79 d (1H, 3-H, J = 7.8 Hz), 7.86 d.d (1H, 4-H, J = 7.8, 7.8 Hz), 8.22 m (2H, Ph), 9.32 s (1H, 5′-H). Mass spectrum: m/z 265.11 (I_{rel} 100%) $[M + H]^+$. Found, %: C 68.22; H 4.51; N 21.06. $C_{15}H_{12}N_4O$. Calculated, %: C 68.17; H 4.58; N 21.20. M 265.11.

6-(4-Methoxyphenyl)-3-(6-methylpyridin-2-yl)-1,2,4-triazine 4-oxide (16c). Yield 103 mg (0.35 mmol, 35%), mp 206–208°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.61 s (3H, Me), 3.88 s (3H, OMe), 7.09 m (2H, H_{arom}), 7.41 d (1H, 5-H, J = 7.8 Hz), 7.81 m (2H, 3-H, 4-H), 8.19 m (2H, H_{arom}), 9.24 s (1H, 5′-H). Mass spectrum: m/z 295.12 (I_{rel} 100%) $[M + H]^+$. Found, %: C 65.12; H 4.82; N 19.08. $C_{16}H_{14}N_4O_2$. Calculated, %: C 65.30; H 4.79; N 19.04. M 295.12.

3-(3-Methylpyridin-2-yl)-6-phenyl-1,2,4-triazine 4-oxide (16d). Yield 132 mg (0.5 mmol, 50%), mp 194–196°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.25 s (3H, Me), 7.49 d.d (1H, 5-H, J = 7.8, 4.8 Hz), 7.56–7.62 m (3H, Ph), 7.80 d.d (1H, 4-H, J = 7.8, 1.0 Hz), 8.21–8.29 m (2H, Ph), 8.55 d.d (1H, 6-H, J = 4.8, 1.0 Hz), 9.39 s (1H, 5′-H). Mass spectrum: m/z 265.11 (I_{rel} 100%) $[M + H]^+$. Found, %: C 68.11; H 4.45; N 21.02. $C_{15}H_{12}N_4O$. Calculated, %: C 68.17; H 4.58; N 21.20. M 265.11.

6-(4-Oxido-6-phenyl-1,2,4-triazin-3-yl)-3-phenylpyridine-2-carbonitrile (16e). Yield 225 mg (0.64 mmol, 64%), mp >250°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.56–7.66 m (6H, Ph), 7.77 m (2H, Ph), 8.26–8.35 m (3H, Ph, Py), 8.49 d (1H, Py, J = 8.0 Hz), 9.46 s (1H, 5′-H). Mass spectrum: m/z 352.12 (I_{rel} 100%) $[M + H]^+$. Found, %: C 71.59; H 3.83; N 20.04. $C_{21}H_{13}N_5O$. Calculated, %: C 71.79; H 3.73; N 19.93. M 352.12.

6-[6-(4-Methylphenyl)-4-oxido-1,2,4-triazin-3-yl]-3-phenylpyridine-2-carbonitrile (16f). Yield 219 mg (0.6 mmol, 60%), mp >250°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.46 s (3H, Me), 7.40 m (2H, C_6H_4), 7.55–7.65 m (3H, Ph), 7.74 m (2H, Ph), 8.17 m (2H, C_6H_4), 8.28 d (1H, Py, J = 8.4 Hz), 8.46 d (1H, Py, J = 8.4 Hz), 9.38 s (1H, 5′-H). Mass spectrum: m/z 366.14 (I_{rel} 100%) $[M + H]^+$. Found, %: C 72.17; H 4.11; N 18.94. $C_{22}H_{15}N_5O$. Calculated, %: C 72.32; H 4.14; N 19.07. M 366.14.

Methyl 6-(4-oxido-6-phenyl-1,2,4-triazin-3-yl)-pyridine-3-carboxylate (16g). A solution of 270 mg

(1.65 mmol) of aldehyde **1f** in ethanol was added to a solution of 270 mg (1.65 mmol) of isonitrosoacetophenone hydrazone in 15 mL of ethanol, and the mixture was kept for 10 h at room temperature. The precipitate was filtered off, washed with ethanol, and dried. We thus isolated 0.41 g (1.32 mmol) of compound **17g** which was dissolved in 40 mL of 1,2-dichloroethane, 1.16 g (13.2 mmol) of activated manganese dioxide was added, and the mixture was stirred for 15 h at room temperature. The inorganic precipitate was filtered off, the filtrate was evaporated under reduced pressure, and the residue was recrystallized from acetonitrile. Yield 210 mg (0.7 mmol, 52%), mp 208–210°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.98 s (3H, OMe), 7.60 m (3H, Ph), 8.23 m (3H, Ph, 5-H), 8.50 d.d (1H, 4-H, J = 8.0, 1.5 Hz), 9.29 d (1H, 2-H, J = 1.5 Hz), 9.36 s (1H, 5′-H). Mass spectrum: m/z 309.10 (I_{rel} 100%) $[M + H]^+$. Found, %: C 62.27; H 3.91; N 18.04. $C_{16}H_{12}N_4O_3$. Calculated, %: C 62.33; H 3.92; N 18.17. M 309.10.

1,2,4-Triazine-5-carbonitriles 19 (*general procedure***).** 1,2,4-Triazine 4-oxide **16a**–**16g**, 0.4 mmol, was dispersed in 15 mL of 1,2-dichloroethane, 55 μL (0.6 mmol) of acetone cyanohydrin and 28 μL (0.2 mmol) of triethylamine were added, and the mixture was stirred for 30 min at 50°C. In the synthesis of **19a** and **19d** the reaction mixture was refluxed for 2 h. The solvent was distilled off under reduced pressure, and the product was isolated by flash chromatography using chloroform as eluent.

3-(6-Bromopyridin-2-yl)-6-phenyl-1,2,4-triazine-5-carbonitrile (19a). Yield 111 mg (0.33 mmol, 83%), mp 158–160°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.65–7.72 m (3H, Ph), 7.87 d (1H, 5-H, J = 7.9 Hz), 8.05 d.d (1H, 4-H, J = 7.9, 7.9 Hz), 8.09–8.13 m (2H, Ph), 8.61 d (1H, 3-H, J = 7.9 Hz). Mass spectrum: m/z 338.00 (I_{rel} 100%) $[M + H]^+$. Found, %: C 53.20; H 2.31; N 20.66. $C_{15}H_8BrN_5$. Calculated, %: C 53.28; H 2.38; N 20.71. M 338.00.

3-(6-Methylpyridin-2-yl)-6-phenyl-1,2,4-triazine-5-carbonitrile (19b). Yield 76 mg (0.28 mmol, 70%), mp 132–134°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.69 s (3H, Me), 7.48 d (1H, 5-H, J = 8.0 Hz), 7.65–7.71 m (3H, Ph), 7.94 d.d (1H, 4-H, J = 8.0, 8.0 Hz), 8.11 m (2H, Ph), 8.39 d (1H, 3-H, J = 8.0 Hz). Mass spectrum: m/z 274.11 (I_{rel} 100%) $[M + H]^+$. Found, %: C 70.23; H 3.90; N 25.48. $C_{16}H_{11}N_5$. Calculated, %: C 70.32; H 4.06; N 25.63. M 274.11.

6-(4-Methoxyphenyl)-3-(6-methylpyridin-2-yl)-1,2,4-triazine-5-carbonitrile (19c). Yield 91 mg (0.3 mmol, 76%), mp 142–144°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.68 s (3H, Me), 3.93 s (3H, OMe), 7.20 m (2H, H_{arom}), 7.46 d (1H, 5-H, J = 8.0 Hz), 7.92 d.d (1H, 4-H, J = 8.0, 8.0 Hz), 8.11 m (2H, H_{arom}), 8.35 d (1H, 3-H, J = 8.0 Hz). Mass spectrum: m/z 304.12 (I_{rel} 100%) $[M + H]^+$. Found, %: C 67.43; H 4.22; N 22.99. $C_{17}H_{13}N_5O$. Calculated, %: C 67.32; H 4.32; N 23.09. M 304.12.

3-(3-Methylpyridin-2-yl)-6-phenyl-1,2,4-triazine-5-carbonitrile (19d). Yield 55 mg (0.2 mmol, 50%), mp 116–118°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.66 s (3H, Me), 7.43 d.d (1H, 5-H, J = 7.8, 4.8 Hz), 7.61–7.69 m (3H, Ph), 7.76 d.d (1H, 4-H, J = 7.8, 1.0 Hz), 8.13–8.19 m (2H, Ph), 8.72 d.d (1H, 6-H, J = 4.8, 1.0 Hz). Mass spectrum: m/z 274.11 (I_{rel} 100%) $[M + H]^+$. Found, %: C 70.17; H 3.87; N 25.69. $C_{16}H_{11}N_5$. Calculated, %: C 70.32; H 4.06; N 25.63. M 274.11.

3-(6-Cyano-5-phenylpyridin-2-yl)-6-(4-methylphenyl)-1,2,4-triazine-5-carbonitrile (19e). Yield 108 mg (0.29 mmol, 73%), mp 228–230°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.51 s (3H, Me), 7.50 m (2H, C_6H_4), 7.60 m (3H, Ph), 7.76 m (2H, Ph), 8.04 m (2H, C_6H_4), 8.38 d (1H, Py, J = 8.4 Hz), 8.89 d (1H, Py, J = 8.4 Hz). Mass spectrum: m/z 375.14 (I_{rel} 100%) $[M + H]^+$. Found, %: C 73.59; H 3.61; N 22.32. $C_{23}H_{14}N_6$. Calculated, %: C 73.78; H 3.77; N 22.45. M 375.14.

Methyl 6-(5-cyano-6-phenyl-1,2,4-triazin-3-yl)-pyridine-3-carboxylate (19f). Yield 82 mg (0.26 mmol, 65%), mp 182–184°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.04 s (3H, OMe), 7.68 m (3H, Ph), 8.19 m (2H, Ph), 8.60 d.d (1H, 4-H, J = 8.0, 2.0 Hz), 8.81 d (1H, 5-H, J = 8.0 Hz), 9.51 d (1H, 2-H, J = 2.0 Hz). Mass spectrum: m/z 318.10 (I_{rel} 100%) $[M + H]^+$. Found, %: C 64.23; H 3.30; N 21.88. $C_{17}H_{11}N_5O_2$. Calculated, %: C 64.35; H 3.49; N 22.07. M 318.10.

This study was performed under financial support by the Russian Science Foundation (project no. 15-13-10 033), by the Council for Grants at the President of the Russian Federation (project no. MK-644.2017.3), and by the Government of the Russian Federation (Program no. 211, contract no. 02.A03.21.0006).

REFERENCES

1. Kozhevnikov, V.N., Shabunina, O.V., Kopchuk, D.S., Ustinova, M.M., Köenig, B., and Kozhevnikov, D.N., *Tetrahedron*, 2008, vol. 64, p. 8963.
2. Kadoma, H., Kawakami, S., Nomura, H., Ushikubo, T., and Seo, S., US Patent no. 2012/178933 A1, 2012.

3. Pfueller, O.C. and Sauer, J., *Tetrahedron Lett*., 1998, vol. 39, p. 8821.
4. Catozzi, N., Bromley, W.J., Wasnaire, P., Gibson, M, and Taylor, R.J.K., *Synlett*, 2007, no. 14, p. 2217.
5. Kopchuk, D.S., Chepchugov, N.V., Kim, G.A., Zyryanov, G.V., Kovalev, I.S., Rusinov, V.L., and Chupakhin, O.N., *Russ. Chem. Bull., Int. Ed*., 2015, vol. 64, p. 695.
6. Altuna-Urquijo, M., Gehre, A., Stanforth, S.P., and Tarbit, B., *Tetrahedron*, 2009, vol. 65, p. 975.
7. Kopchuk, D.S., Nikonov, I.L., Zyryanov, G.V., Kovalev, I.S., Rusinov, V.L., and Chupakhin, O.N., *Chem. Heterocycl. Compd*., 2014, vol. 50, p. 907.
8. Kopchuk, D.S., Khasanov, A.F., Kovalev, I.S., Kim, G.A., Nikonov, I.L., Zyryanov, G.V., Rusinov, V.L., and Chupakhin, O.N., *Chem. Heterocycl. Compd*., 2014, vol. 50, p. 864.
9. Nikonov, I.L., Kopchuk, D.S., Kovalev, I.S., Zyryanov, G.V., Khasanov, A.F., Slepukhin, P.A., Rusinov, V.L., and Chupakhin, O.N., *Tetrahedron Lett*., 2013, vol. 54, p. 6427.
10. Kopchuk, D.S., Nikonov, I.L., Zyryanov, G.V., Nosova, E.V., Kovalev, I.S., Slepukhin, P.A., Rusinov, V.L., and Chupakhin, O.N., *Mendeleev Commun*., 2015, vol. 25, p. 13.
11. Kopchuk, D.S., Nikonov, I.L., Zyryanov, G.V., Kovalev, I.S., Taniya, O.S., Rusinov, V.L., and Chupakhin, O.N., *Russ. J. Org. Chem*., 2015, vol. 51, p. 1170.
12. Prokhorov, A.M., Kozhevnikov, D.N., Rusinov, V.L., Chupakhin, O.N., Glukhov, I.V., Antipin, M.Yu., Kazheva, O.N., Chekhlov, A.N., and Dyachenko, O.A., *Organometallics*, 2006, vol. 25, p. 2972.
13. Kozhevnikov, D.N., Kozhevnikov, V.N., Prokhorov, A.M., Ustinova, M.M., Rusinov, V.L., Chupakhin, O.N., Aleksandrov, G.G., and Köenig, B., *Tetrahedron Lett*., 2006, vol. 47, p. 869.
14. Kovalev, I.S., Kopchuk, D.S., Khasanov, A.F., Zyryanov, G.V., Rusinov, V.L., and Chupakhin, O.N., *Mendeleev Commun*., 2014, vol. 24, p. 117.
15. Dawson, M.V and Lyle, S.J., *Talanta*, 1990, vol. 37, p. 1189.
16. Ueno, Y., Morishita, K., Muraoka, M., and Ohashi, N., US Patent no. 6159974, 2000.
17. Lewis, F.W., Harwood, L.M., and Hudson, M.J., WO Patent no. 2011077081, 2011.
18. Kozhevnikov, V.N., Kozhevnikov, D.N., Nikitina, T.V., Rusinov, V.L., Chupakhin, O.N., Zabel, M., and Koenig, B., *J. Org. Chem*., 2003, vol. 68, p. 2882.
19. Prokhorov, A.M., Kozhevnikov, V.N., Kopchuk, D.S., Bernard, H., Le Bris, N., Tripier, R., Handel, H., Koenig, B., and Kozhevnikov, D.N., *Tetrahedron*, 2011, vol. 67, p. 597.
20. Kozhevnikov, V.N., Kozhevnikov, D.N., Shabunina, O.V., Rusinov, V.L., and Chupakhin, O.N., *Tetrahedron Lett*., 2005, vol. 46, p. 1791.
21. Kopchuk, D.S., Krinochkin, A.P., Kozhevnikov, D.N., and Slepukhin, P.A., *Polyhedron*, 2016, vol. 118, p. 30.
22. Iqbal, N., Akula, M.R., Vo, D., Matowe, W.C., McEwen, C.-A., Wolowyk, M.W., and Knaus, E.E., *J. Med. Chem*., 1998, vol. 41, p. 1827.
23. Chigir', A.N., Novikova, V.F., Kalikhman, I.D., Chumakov, Yu.I., Cherkashin, M.I., and Berlin, A.A., *Polymer Sci. USSR*, 1969, vol. 11, p. 2053.
24. Yamazaki, T., Saitou, A., Ono, M., Yokoyama, S., Bannai, K., Hirose, K., and Yanaka, M., EP Patent no. 1431290 A1, 2004.
25. Thallaj, N.K., Przybilla, J., Welter, R., and Mandon, D., *J. Am. Chem. Soc*., 2008, vol. 130, p. 2414.
26. Kozhevnikov, D.N., Kozhevnikov, V.N., Rusinov, V.L., Chupakhin, O.N., Sidorov, E.O., and Klyuev, N.A., *Russ. J. Org. Chem*., 1998, vol. 34, p. 393.
27. Chupakhin, O.N., Rusinov, V.L., Ulomsky, E.N., Kojevnikov, D.N., and Neunhoeffer, H., *Mendeleev Commun*., 1997, vol. 7, p. 66.
28. Dey, B.B., *J. Chem. Soc*., 1914, vol. 105, p. 1039.
29. Ashimori, A., Ono, T., Uchida, T., Ohtaki, Y., Fukaya, C., Watanabe, M., and Yokoyama, K., *Chem. Pharm. Bull*., 1990, vol. 38, p. 2446.