# Synthesis of 6-R-isoxazolo[4,3-*b*]pyridines and their reactions with *C*-nucleophiles*

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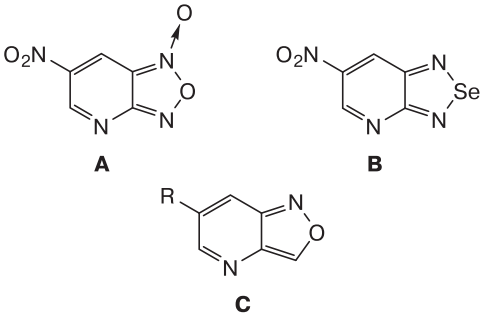
Available 2-chloro-3-nitropyridines were used to synthesize new representatives of 6-substituted 3-benzoylisoxazolo[4,3-*b*]pyridines, which were found to react with neutral *C*-nucleophiles to give 1,4-addition products.

**Key words:** nitro group, nitropyridines, nucleophilic addition, dihydropyridines, dearomatization.

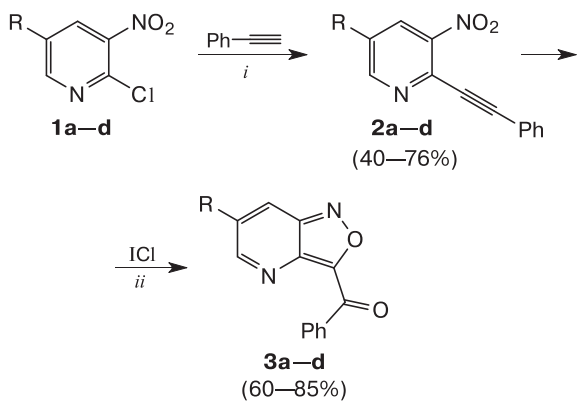
Dihydropyridine derivatives are an important class of organic compounds. The dihydropyridine ring is part of a representative series of natural and synthetic compounds, many of which exhibit biological activity.[1,2] One of the most popular methods for the synthesis of dihydropyridine derivatives is the dearomatization of various functionalized pyridines.[3] Dearomatization as a synthetic method for functionally complex saturated structures possesses an enormous synthetic potential and consists in the transformation of available and simple aromatic compounds to functionally complex, poorly available, and promising intermediate products.[3—9] Since the mid-1990s, the interest in such processes and their synthetic application has been steadily growing.

The present work is a continuation of our research on the application of the dearomatization strategy in the synthesis of new multifunctional azaheterocycles.[10—18] Earlier, we have shown that nitropyridines annulated with π-deficient heterocycles (furoxan **A** and selenadiazole **B**) react with neutral nucleophiles to form addition products, namely, derivatives of 1,4-dihydropyridine.[16,17] Isoxazolo[4,3-*b*]pyridine derivatives **C** are among the available bicycles closest to heterocyclic systems **A** and **B** in the structure and electron-deficient character. In this connection, the present work is devoted to the synthesis of pyridine derivatives fused with the isoxazole ring and study of their reactions with nucleophiles.




Available 2-chloro-3-nitropyridines **1a—d** were used as the starting compounds, which were introduced into the cross-coupling reactions with phenylacetylene. The cycloisomerization of compounds **2a—d** in the presence of catalytic amounts of ICl led to the target isoxazolo[4,3-*b*]pyridines **3a—d** in good yields (Scheme 1).

**Scheme 1**




R = Cl (**a**), H ( **b**), $CO_2Me$ (**c**), $NO_2$ (**d**)

**Reagents and conditions:** *i*. $Et_3N$, THF, CuI, $Pd(Ph_3)_2Cl_2$, 40 °C; *ii*. $CH_2Cl_2$, Δ.

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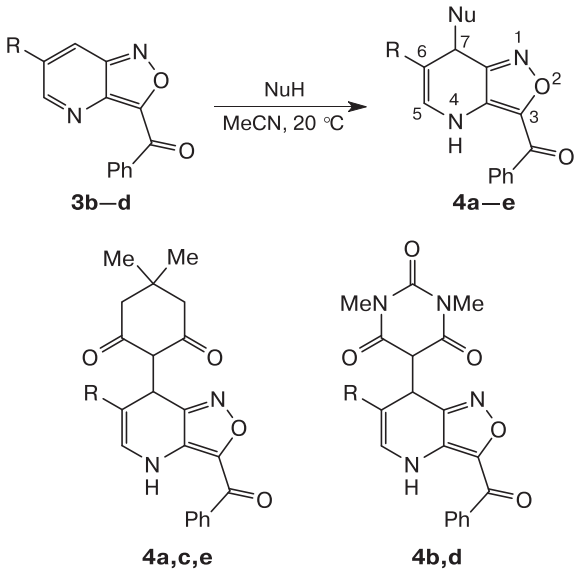
We studied the reactions of isoxazolopyridines **3a—d** with *C*-nucleophiles (dimedone and 1,3-dimethylbarbituric acid). It was found that 6-chloroisoxazolo[4,3-*b*]-pyridine (**3a**) does not give addition products even under drastic conditions (80 °C). At the same time, 6-unsubstituted isoxazolopyridine **3b** is capable of forming an adduct with dimedone **4e** (Scheme 2). However, unlike compounds **A** and **B**, which react with dimedone within a few minutes, a complete conversion of **3b** requires 4 h. For isoxazolopyridines **3c** and **3d** with electron-withdrawing substituents at position 6, the reaction proceeded much easier (less than within 1 h) resulting in good yields of dihydroisoxazolopyridines **4a—e**.

**Scheme 2**




| 4 | R | Yield (%) | 4 | R | Yield (%) |
|---|---|---|---|---|---|
| **a** | $NO_2$ | 79 | **d** | Me(O)OC | 75 |
| **b** | $NO_2$ | 85 | **e** | H | 70 |
| **c** | Me(O)OC | 87 | | | |

The structure of the synthesized compounds was established based on the NMR spectroscopy and high resolution mass spectrometry data. The $^1$H NMR spectra of adducts **4a—e** exhibit signals corresponding to the H(7) protons in the region of δ 5.0—5.5, as well as low-field doublets for the NH (δ 9.8—10.4) and H(5) protons (δ 8.1) with close spin-spin coupling constants, which confirms the addition of the nucleophile at position 7. This is consistent with the results obtained earlier for the adducts with other azolopyridines.[16,17]

In conclusion, a series of new 6-substituted 3-benzoylisoxazolo[4,3-*b*]pyridines were synthesized based on the Sonogashira reaction of phenylacetylene with 2-chloro-3-nitropyridines and subsequent cycloisomerization. 6-R-Isoxazolo[4,3-*b*]pyridines were found to react with neutral *C*-nucleophiles without assistance with a base or a catalyst. The reaction is accompanied by dearomatization of the pyridine ring to give 1,4-addition products.

## Experimental

Melting points were measured on a Stuart SMP20 apparatus. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AM-300 ($^1$H, 300 MHz; $^{13}$C, 75 MHz), Bruker Avance DRX 500 ($^1$H, 500 MHz; $^{13}$C, 125 MHz), Bruker Avance II 600 instruments ($^1$H, 600 MHz; $^{13}$C, 150 MHz). All the experiments were performed according to standard Bruker procedures. Chemical shifts are given relative to $Me_4Si$. Samples for NMR spectroscopy were prepared in DMSO-$d_6$ or $CDCl_3$. High resolution mass spectra (HRMS) were recorded on a Bruker maXis instrument using electrospray ionization (ESI). The measurements were performed in the positive ion mode (capillary voltage 4500 V). The mass scan range at *m/z* 50—3000 Da, an external calibration with Electrospray Calibrant Solution (Fluka). Solutions of compounds in acetonitrile were syringed at the flow rate of 3 μL min$^{-1}$. The nebulizer gas nitrogen (4 L min$^{-1}$), the interface temperature 180 °C. Reaction progress and purity of compounds were monitored by TLC on Silica gel 60 F254 plates (Merk). Compounds **1a—d** are commercially available (ABCR catalog). Compounds **2b** and **3b** were synthesized according to the described procedure.[19]

**Synthesis of compounds 2a—d (general procedure).** A mixture of the corresponding chloride **1** (5 mmol), $PdCl_2(PPh_3)_2$ (0.175 g, 0.25 mmol), and $Et_3N$ (1.4 mL, 10 mmol) was suspended in anhydrous THF (20 mL). Then phenylacetylene (0.66 mL, 6 mmol) and CuI (0.025 g, 0.13 mmol) were added under argon. The reaction mixture was stirred in an argon atmosphere for 2—4 h at 40 °C (the reaction completion was detected by TLC). Then the solvent was evaporated under reduced pressure. The residue was purified by column chromatography ($SiO_2$—$CHCl_3$).

**5-Chloro-3-nitro-2-(phenylethynyl)pyridine (2a).** The yield was 0.52 g (40%). M.p. 103—105 °C. $^1$H NMR ($CDCl_3$), δ: 7.41—7.48 (m, 3 H, Ph); 7.69—7.71 (d, 2 H, Ph, $J$ = 6.8 Hz); 8.41 (d, 1 H, C(4)H, $J$ = 1.6 Hz); 8,81 (d, 1 H, C(6)H, $J$ = 1.6 Hz). $^{13}$C NMR ($CDCl_3$), δ: 84.3, 99.1, 121.2, 128.6, 130.3, 130.8, 132.2, 132.6, 135.4, 142.0, 145.7, 146.4, 152.6. HRMS (ESI): found *m/z* 259.0259; calculated for $C_{13}H_7ClN_2O_2$ $[M + H]^+$ 259.0269.

**3-Nitro-2-(phenylethynyl)pyridine (2b).** The yield was 0.92 g (82%). M.p. 107—109 °C (see Ref. 24: 107—109 °C). $^1$H NMR ($CDCl_3$), δ: 7.42—7.51 (m, 4 H, ArH); 7.70—7.73 (m, 2 H, ArH); 8.42 (dd, 1 H, C(4)H, $J$ = 8.1 Hz, $J$ = 1.2 Hz); 8.84 (d, 1 H, C(6)H, $J$ = 3.6 Hz).

**Methyl 5-nitro-6-(phenylethynyl)nicotinate (2c).** The yield was 1.07 g (76%). M.p. 117—119 °C. $^1$H NMR ($CDCl_3$), δ: 4.05 (s, 3 H, Me); 7.42—7.52 (m, 3 H, Ph); 7.71—7.74 (d, 2 H, Ph, $J$ = 7.2 Hz); 8.95 (d, 1 H, C(4)H, $J$ = 1.3 Hz); 9.39 (d, 1 H, C(6) H, $J$ = 1.3 Hz). $^{13}$C NMR ($CDCl_3$), δ: 53.9, 86.0, 102.0, 121.6, 125.6, 129.4, 131.4, 133.6, 134.1, 141.1, 147.1, 154.5, 164.1. HRMS (ESI): found *m/z* 283.0721; calculated for $C_{15}H_{10}N_2O_4$ $[M + H]^+$ 283.0713.

**3,5-Dinitro-2-(phenylethynyl)pyridine (2d).** The yield was 0.97 g (72%). M.p. 183—185 °C. $^1$H NMR ($CDCl_3$), δ: 7.45—7.54 (m, 3 H, Ph); 7.74—7.76 (d, 2 H, Ph, $J$ = 7.2 Hz); 9.17 (s, 1 H,

C(4)H); 9.63 (s, 1 H, C(6)H). $^{13}$C NMR (DMSO-$d_6$), δ: 64.0, 85.0, 100.8, 119.8, 128.7, 129.2, 131.3, 132.4, 142.3, 146.2, 148.3. HRMS (ESI): found *m/z* 270.0514; calculated for $C_{13}H_7N_3O_4$ $[M + H]^+$ 270.0509.

**Synthesis of compounds 3a—d (general procedure).** The reagent ICl (16 mg, 0.1 mmol) was added to a solution of the corresponding acetylene **2** (2 mmol) in $CH_2Cl_2$ (20 mL). The reaction mixture was refluxed with stirring for 4—8 h (TLC monitoring). Then, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography ($SiO_2$—$CH_2Cl_2$).

**6-Chloroisoxazolo[4,3-*b*]pyridin-3-yl(phenyl)methanone (3a).** The yield was 0.31 g (60%). M.p. 120—122 °C. $^1$H NMR ($CDCl_3$), δ: 7.61 (t, 2 H, Ph, *J* = 7.6 Hz); 7.74 (t, 1 H, Ph, *J* = 7.4 Hz); 8.14 (d, 1 H, C(4)H, *J* = 1.7 Hz); 8.23 (d, 2 H, Ph, *J* = 7.5 Hz); 8.71 (s, 1 H, C(6)H). $^{13}$C NMR ($CDCl_3$), δ: 121.6, 128.3, 128.8, 130.3, 130.4, 131.8, 133.6, 134.5, 135.5, 151.3, 155.3, 161.0, 180.7. HRMS (ESI): found *m/z* 259.0276; calculated for $C_{13}H_7ClN_2O_2$ $[M + H]^+$ 259.0269.

**Isoxazolo[4,3-*b*]pyridin-3-yl(phenyl)methanone (3b).** The yield was 0.36 g (80%). M.p. 95—96 °C (see Ref. 24: 95—96 °C). $^1$H NMR ($CDCl_3$), δ: 7.37 (dd, 1 H, C(6)H, *J* = 9.2 Hz, *J* = 3.6 Hz); 7.54—7.59 (m, 2 H, ArH); 7.66—7.71 (m, 1 H, C(4)H); 8.20—8.23 (m, 2 H, ArH); 8.84 (dd, 1 H, C(5)H, *J* = 3.6 Hz, *J* = 1.5 Hz).

**Methyl 3-benzoylisoxazolo[4,3-*b*]pyridin-6-carboxylate (3c).** The yield was 0.37 g (65%). M.p. 114—116 °C. $^1$H NMR ($CDCl_3$), δ: 4.07 (s, 3 H, Me); 7.61 (t, 2 H, Ph, *J* = 7.6 Hz); 7.74 (t, 1 H, Ph, *J* = 7.4 Hz); 8.25 (d, 2 H, Ph, *J* = 7.5 Hz); 8.85 (d, 1 H, C(4)H, *J* = 1.7 Hz); 9.36 (d, 1 H, C(6)H, *J* = 1.7 Hz). $^{13}$C NMR ($CDCl_3$), δ: 53.2, 127.5, 127.7, 128.8, 130.5, 134.4, 134.5, 135.6, 150.7, 154.9, 161.3, 164.1, 180.8. HRMS (ESI); found *m/z* 283.0709; calculated for $C_{15}H_{10}N_2O_4$ $[M + H]^+$ 283.0713.

**6-Nitroisoxazolo[4,3-*b*]pyridin-3-yl(phenyl)methanone (3d).** The yield was 0.46 g (85%). M.p. 135—137 °C. $^1$H NMR ($CDCl_3$), δ: 7.63 (t, 2 H, Ph, *J* = 7.7); 7.77 (t, 1 H, Ph, *J* = 7.4); 8.23 (d, 2 H, Ph, *J* = 7.4 Hz); 9.08 (d, 1 H, C(4)H, *J* = 2.2 Hz); 9.55 (d, 1 H, C(6)H, *J* = 2.2 Hz). $^{13}$C NMR ($CDCl_3$), δ: 122.7, 129.7, 131.2, 134.9, 135.7, 135.9, 144.7, 149.6, 150.4, 163.0, 181.1. HRMS (ESI): found *m/z* 270.0508; calculated for $C_{13}H_7N_3O_4$ $[M + H]^+$ 270.0509.

**Synthesis of compounds 4a—e (general procedure).** A corresponding CH-acid (1 mmol) was added to a solution of isoxazole **3** (1 mmol) in anhydrous $CH_3CN$ (5 mL). The reaction mixture was stirred at room temperature for 1—4 h (TLC monitoring). After completion of the reaction, the solution was poured into water (25 mL), the precipitate formed was collected by filtration and dried in air.

**2-(Benzoyl-6-nitro-4,7-dihydroisoxazolo[4,3-*b*]pyridin-7-yl)-5,5-dimethylcyclohexane-1,3-dione (4a).** The yield was 0.29 g (79%). M.p. 244—246 °C. $^1$H NMR (DMSO-$d_6$), δ: 0.93 (s, 6 H, 2 Me); 2.25 (br.s, 5 H, 2 $CH_2$); 5.75 (br.s, 1 H, H(7)); 7.64 (t, 2 H, Ph, *J* = 7.5 Hz); 7.75 (t, 1 H, Ph, *J* = 7.3 Hz); 8.01 (d, 1 H, H(5), *J* = 5.7 Hz); 8.13 (d, 2 H, Ph, *J* = 7.7 Hz); 10.55 (d, NH, *J* = 6.1 Hz). $^{13}$C NMR (DMSO-$d_6$), δ: 28.5, 29.5, 33.0, 43.7, 51.0, 127.9, 130.2, 130.5, 135.3, 136.3, 138.7, 147.5, 158.6, 181.9. HRMS (ESI): found *m/z* 410.1340; calculated for $C_{21}H_{19}N_3O_6$ $[M + H]^+$ 410.1347.

**5-(3-Benzoyl-6-nitro-4,7-dihydroisoxazolo[4,3-*b*]pyridin-7-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4b).** The yield was 0.36 g (85%). M.p. 234—235 °C. $^1$H NMR (DMSO-$d_6$), δ: 3.04 (s, 3 H, Me); 3.17 (s, 3 H, Me); 4.65 (s, 1 H, CH); 5.52 (s, 1 H, H(7)); 7.64 (t, 2 H, Ph, *J* = 7.2 Hz); 7.75 (d, 1 H, Ph, *J* = 6.8 Hz); 8.13 (d, 3 H, Ph and H(5) , *J* = 7.1 Hz); 10.93 (d, 1 H, NH, *J* = 3.7 Hz). $^{13}$C NMR (DMSO-$d_6$), δ: 28.6, 28.8, 34.2, 34.3, 52.9, 123.6, 124.6, 129.5, 129.9, 134.9, 140.2, 151.6, 156.8, 166.7, 167.0, 167.1, 169.9, 171.8, 181.1. HRMS (ESI): found *m/z* 426.1037; calculated for $C_{19}H_{15}N_5O_7$ $[M + H]^+$ 426.1044.

**Methyl 3-benzoyl-7-(4,4-dimethyl-2,6-dioxocyclohexyl)-4,7-dihydroisoxazolo[4,3-*b*]pyridin-6-carboxylate (4c).** The yield was 0.37 g (87%). M.p. 232—234 °C. $^1$H NMR (DMSO-$d_6$), δ: 0.93 (s, 6 H, 2 Me); 2.16 (br.s, 4 H, 2 $CH_2$); 3.53 (s, 3 H, $CO_2Me$); 5.36 (s, 1 H, H(7)); 7.33 (s, 1 H, H(5)); 7.61 (t, 2 H, Ph, *J* = 7.3 Hz); 7.70 (d, 1 H, Ph, *J* = 7 Hz); 8.11 (d, 2 H, Ph, *J* = 7.6 Hz); 9.73 (d, NH, *J* = 5 Hz). $^{13}$C NMR (DMSO-$d_6$), δ: 26.0, 27.1, 28.0, 31.7, 50.7, 102.6, 128.7, 128.8, 129.0, 133.7, 135.6, 136.6, 136.7, 144.5, 157.4, 166.3, 180.4. HRMS (ESI): found *m/z* 423.1545; calculated for $C_{23}H_{22}N_2O_6$ $[M + H]^+$ 423.1551.

**Methyl 3-benzoyl-7-(1,3-dimethyl-2,4,6-trioxahexahydropyrimidin-5-yl)-4,7-dihydroisoxazolo[4,3-*b*]pyridin-6-carboxylate (4d).** The yield was 0.33 g (75%). M.p. 170—172 °C. $^1$H NMR (DMSO-$d_6$), δ: 3.03 (s, 3 H, Me); 3.13 (s, 3 H, Me); 3.63 (s, 3 H, $CO_2Me$); 4.43 (s, 1 H, CH); 5.07 (s, 1 H, H(7)); 7.44 (d, 1 H, H(5), *J* = 5.4 Hz); 7.63 (t, 2 H, Ph, *J* = 7.3 Hz); 7.74 (t, 1 H, Ph, *J* = 7.0 Hz); 8.12 (d, 2 H, Ph, *J* = 7.7 Hz); 10.2 (d, 1 H, NH, *J* = 5.3 Hz). $^{13}$C NMR (DMSO-$d_6$), δ: 28.5, 28.6, 33.7, 51.8, 54.5, 99.6, 127.7, 129.5, 129.7, 134.5, 135.7, 139.4, 151.8, 166.8, 167.3, 181.0. HRMS (ESI): found *m/z* 439.1242; calculated for $C_{21}H_{18}N_4O_7$ $[M + H]^+$ 439.1248.

**2-(Benzoyl-4,7-dihydroisoxazolo[4,3-*b*]pyridin-7-yl)-5,5-dimethylcyclohexane-1,3-dione (4e).** The yield was 0.25 g (70%). M.p. 180—182 °C. $^1$H NMR (DMSO-$d_6$), δ: 0.91 (s, 3 H, Me); 0.99 (s, 3 H, Me); 2.08—2.40 (m, 4 H, 2 $CH_2$); 4.33 (s, 1 H, CH); 5.76 (s, 1 H, H(7)); 7.59—7.68 (m, 4 H, Ph and C(5)H); 8.07—8.09 (d, 2 H, Ph, *J* = 6.4 Hz); 8.45 (s, 1 H, H(5)). $^{13}$C NMR (DMSO-$d_6$), δ: 19.4, 24.6, 27.0, 28.5, 31.9, 41.3, 49.7, 77.0, 110.4, 124.2, 126.8, 128.7, 128.8, 128.9, 130.3, 133.2, 134.4, 156.5, 169.5, 180.0, 194.2. HRMS (ESI): found 365.1494; calculated for $C_{21}H_{20}N_2O_4$ $[M + H]^+$ 365.1496.

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## References

1. V. K. Sharma, S. K. Singh, *RSC Adv.*, 2017, **7**, 2682.
2. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
3. G. Bertuzzi, L. Bernardi, M. Fochi, *Catalysts*, 2018, **8**, 632.
4. G. Ramachandran, K. I. Sathiyanarayanan, *Curr. Organocatal.*, 2015, **2**, 14.
5. A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro, T. Marks, *J. Nat. Chem.*, 2014, **6**, 1100.
6. S. P. Roche, Jr., J. A. Porco, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068.
7. P. L. Smith, M. D. Chordia, W. D. Harman, *Tetrahedron*, 2001, **57**, 8203.
8. W. C. Wertjes, E. H. Southgate, D. Sarlah, *Chem. Soc. Rev.*, 2018, **47**, 7996.

9. V. N. Charushin, O. N. Chupakhin, *Russ. Chem. Bull.*, 2019, **68**, 453.
10. L. S. Konstantinova, M. A. Bastrakov, A. M. Starosotnikov, I. V. Glukhov, K. A. Lysov, O. A. Rakitin, S. A. Shevelev, *Mendeleev Commun.*, 2010, **20**, 353.
11. M. A. Bastrakov, A. I. Leonov, A. M. Starosotnikov, I. V. Fedyanin, S. A. Shevelev, *Russ. Chem. Bull.*, 2013, **62**, 1052.
12. M. A. Bastrakov, A. M. Starosotnikov, I. V. Fedyanin, V. V. Kachala, S. A. Shevelev, *Mendeleev Commun.*, 2014, **24**, 203.
13. M. A. Bastrakov, A. M. Starosotnikov, A. A. Pavlov, I. L. Dalinger, S. A. Shevelev, *Chem. Heterocycl. Compd.*, 2016, **52**, 690.
14. A. M. Starosotnikov, M. A. Bastrakov, A. A. Pavlov, I. V. Fedyanin, I. L. Dalinger, S. A. Shevelev, *Mendeleev Commun.*, 2016, **26**, 217.
15. M. A. Bastrakov, A. Yu. Kucherova, A. K. Fedorenko, A. M. Starosotnikov, I. V. Fedyanin, I. L. Dalinger, S. A. Shevelev, *Arkivoc,* 2017, **iii**, 181.
16. A. M. Starosotnikov, D. V. Shkaev, M. A. Bastrakov, I. V. Fedyanin, S. A. Shevelev, I. L. Dalinger, *Beilstein J. Org. Chem.*, 2017, **13**, 2854.
17. A. M. Starosotnikov, D. V. Shkaev, M. A. Bastrakov, S. A. Shevelev, I. L. Dalinger, *Mendeleev Commun.*, 2018, **28**, 638.
18. M. A. Bastrakov, A. K. Fedorenko, A. M. Starosotnikov, V. V. Kachala, S. A. Shevelev, *Chem. Heterocycl. Compd.*, 2019, **55**, 72.
19. I. Cikotiene, *Eur. J. Org. Chem.*, 2012, 2766.

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