Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2019, **29**, 50–52

Mendeleev Communications

A catalyst-free one-step synthesis of *N*-pyrimidinyl amidines from endocyclic enamines and 4-azidopyrimidines

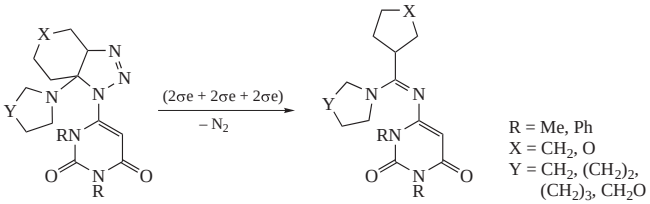
Nikolai A. Beliaev,[a] Tetyana V. Beryozkina,[a] Gert Lubec[b] and Vasiliy A. Bakulev*[a]

[a] *Institute of Chemical Engineering, Ural Federal University, 620002 Ekaterinburg, Russian Federation. E-mail: v.a.bakulev@urfu.ru*

[b] *Neuroproteomics, Paracelsus Medical University, 5020 Salzburg, Austria*

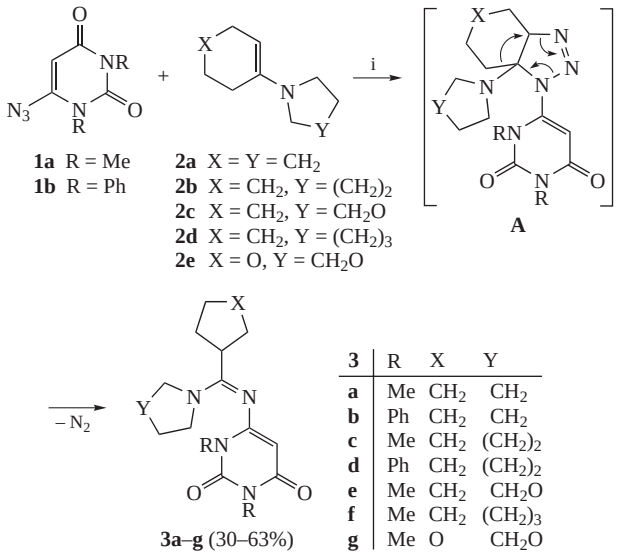
DOI: 10.1016/j.mencom.2019.01.015

Novel *N*-pyrimidyl amidines of alycyclic acids were obtained in one step from of 4-azidopyrimidines and endocyclic enamines. The reaction mechanism involves [3 + 2]-addition of azide at the double bond followed by cleavage of thus formed 1,2,3-triazoline ring, and a contraction of alicycle.



Many biologically active and natural compounds contain amidine structural fragment.[1] On the other hand, pyrimidine derivatives exhibit chemotherapeutic activities.[2–6] Some *N*-pyrimidyl amidines, mainly *N*-alkyl and *N*-aryl derivatives, are documented.[7] To the best of our knowledge, the data on *N*-pyrimidyl amidines of alicyclic acids are lacking so far. An introduction of an alicyclic ring to an amidine molecule would increase its lipophilicity and enhance transport through a cellular membrane. Therefore, it seems challenging to elaborate an access to *N*-pyrimidinyl-substituted amidines bearing an alicyclic counterpart.

Basing on our experience in the synthesis of *N*-sulfonyl- and 4-nitroimidazol-5-yl-containing amidines from enamines and the corresponding azides,[8] herein we anticipated to obtain *N*-pyrimidinyl amidines of alicyclic acids by the reaction of 5-azidopyrimidines with enamines. Note that main reaction directions for (hetero)aromatic azides and enamines are the formation of 1,2,3-triazoline and 1,2,3-triazole rings,[8(b),9] and only a few examples leading to *N*-(hetero)aryl amidines are known so far.[9(b)]



3	R	X	Y
a	Me	CH_2	CH_2
b	Ph	CH_2	CH_2
c	Me	CH_2	$(CH_2)_2$
d	Ph	CH_2	$(CH_2)_2$
e	Me	CH_2	CH_2O
f	Me	CH_2	$(CH_2)_3$
g	Me	O	CH_2O

Scheme 1 *Reagents and conditions*: i, 1,4-dioxane, ~20 °C, 24 h.

In our experiments reaction of 7-azidopyrimidine-2,4-(1*H*,3*H*)-diones **1a**,**b** with endocyclic enamines of type **2a**–**e** afforded *N*-pyrimidinyl amidines **3a**–**g** with good selectivity (Scheme 1).† Despite of the possibility of the formation of several products, we have found that reaction of azide **1a** with enamine **2a** in anhydrous 1,4-dioxane at 23–25 °C for 24 h proceeded selectively to form single amidine **3a** in 62% yield.

Replacement of 1,4-dioxane by methanol, ethanol or toluene leads to decrease in the product yield and formation of tar-like products. Cooling to 13 °C decelerates the reaction retaining the yield of amidine **3a**. With optimal conditions in hand we carried out the reaction with other reactants (see Scheme 1) and prepared various amidines **3a**–**g** containing cyclopentane, pyrrolidine, piperidine and morpholine rings. The quality of enamine **2d** bearing azepane ring, which we could prepare, was not good enough for its conversion into amidine **3f** by the reaction with azide **1a**, and the mixture of several unseparable compounds was

† *General procedure for the synthesis of amidines* **3a**–**e**,**g**. A mixture of azide **1** (1 mmol) and enamine **2** (1.25 mmol) in 1,4-dioxane (2–4 ml) was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography with silica gel (chloroform–ethanol, 10:1; ethyl acetate–ethanol, 10:1) or crystallized from minimal amount of methanol (**3g**).

*6-{[(*E*)-Cyclopentyl(pyrrolidin-1-yl)methylidene]amino}-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione* **3a**. Yield 190 mg (62%), yellow powder, mp 100–105 °C, R_f 0.30 (ethyl acetate–ethanol, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50–1.69 (m, 2H, $CH_2^{cyclopent}$), 1.69–1.85 (m, 4H, $CH_2^{cyclopent}$ + CH_2^{pyrrol}), 1.85–2.08 (m, 6H, 2$CH_2^{cyclopent}$ + CH_2^{pyrrol}), 2.98 (p, 1H, $CH^{cyclopent}$, *J* 8.2 Hz,), 3.33 (s, 3H, NMe), 3.29 (s, 3H, NMe), 3.42 (br.s, 4H, 2NCH_2^{pyrrol}), 4.67 (s, 1H, CH^{pyrim}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1 (2CH_2^{pyrrol}), 26.0 (2$CH_2^{cyclopent}$), 27.5 (NMe), 30.3 (NMe), 30.7 (2$CH_2^{cyclopent}$), 43.1 ($CH^{cyclopent}$), 49.2 (2NCH_2^{pyrrol}), 84.6 (CH^{pyrim}), 152.7 (C=O), 155.8 ($C4^{pyrim}$), 163.4 (C=O), 163.8 ($C^{amidine}$). MS (EI), *m*/*z* (%): 304 $[M]^+$ (33), 265 (25), 235 (20), 140 (100), 82 (46), 55 (61). IR (NPVO, ZnSe, ν/cm^{-1}): 1131, 1342, 1419, 1574, 1644, 1692, 2872, 2945. Found (%): C, 63.16; H, 8.04; N, 18.19. Calc. for $C_{16}H_{24}N_4O_2$ (%): C, 63.13; H, 7.95; N, 18.41.

obtained. The desired amidine **3f** was prepared in 40% yield by three-component reaction of azide **1a** with a mixture of cyclohexanone and azepane through *in situ* formation of enamine **2d**.‡

Synthesis of compound **3g** was performed both by reaction of azide **1a** with enamine **2e** and by three-component reaction of azide **1a** with tetrahydropyran-4-one and morpholine in 62 and 30% yields, respectively.§ Therefore, we can conclude that synthesis of amidines **3** where pure enamines **2** are involved in the reaction with azides **1** is more effective in comparison with three-component method. Probably the formation of water from reaction of a ketone and a secondary amine interferes with the reaction between azide **1** and enamine **2**. The structures of compounds **3** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The signals in ^{13}C NMR spectra for amidine carbon, C^2 and C^4 of carbonyl carbons of pyrimidine ring were observed in the ranges of 160.3–164.0, 163.2–163.5 and 152.2–152.6 ppm, respectively. Finally, the structures of representative amidine **3g** was confirmed by the single crystal X-ray diffraction study (Figure 1).¶

Interesting feature of reaction between azides **1** and enamines **2** is the contraction of a six-membered cycle of enamine ring to five-membered one.[9(*b*)] Contraction of tetrahydropyran to tetrahydrofuran ring in reaction of azides with enamines is first observed in the current study. It is worth to mention that the single work on metal-catalytic transformation of tetrahydropyran to furan was published.[10]

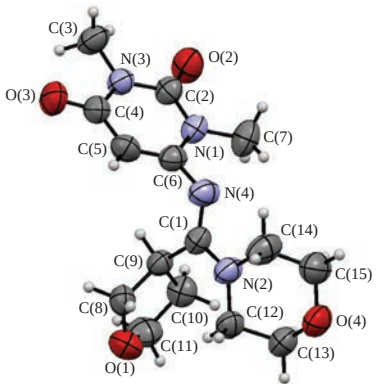


Figure 1 Molecular structure of amidine **3g** in the thermal ellipsoids of 50% probability.

The plausible mechanism for reaction of azides **1** with endocyclic enamines **2** leading to amidine **3** *via* unstable intermediate 1,2,3-triazolines **A** (see Scheme 1) is in accordance with our previous work on the reaction of other azides with endocyclic enamines.[8(*a*)] A few examples of stable triazolines obtained by reaction of enamines with azides were reported[9(*b*)] confirming the mechanism. The last step includes elimination of dinitrogen accompanied with the shift of C–C bond of cyclohexane (tetrahydropyran) ring to form cyclopentane (terahydrofuran) ring in amidine **3**. The similar mechanism confirmed by quantum calculations was described for the reactions of sulfonyl azides with enamines leading to *N*-sulfonyl amidines.[11]

In conclusion, the reaction of 7-azidopyrimidine-1,3-diones with various endocyclic enamines was shown to occur under mild conditions to selectively afford novel *N*-pyrimidinyl amidines. The reaction involves the formation of intermediate 1-pyrimidyl-1,2,3-triazolines, cleavage of 1,2,3-triazoline ring and contraction of the cycle.

This work was supported by the Russian Science Foundation (project no. 18-13-00161).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.015.

References

1 (*a*) J. V. Greenhill and P. Lue, *Prog. Med. Chem.*, 1993, **30**, 203; (*b*) G. V. Boyd, in *Chemistry of Amidines and Imidates*, eds. S. Patai and Z. Rappoport, Wiley, New York, 1991, vol. 2, ch. 8.3, pp. 367–424.

‡ *6-{(*E*)-[(Azepan-1-yl)(cyclopentyl)methylidene]amino}-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione* **3f**. Azide **1a** (181 mg, 1 mmol) was added to the mixture of azepane (150 mg, 1.51 mmol) and cyclohexanone (165 mg, 1.68 mmol) in 1,4-dioxane (2 ml), and the resulting mixture was stirred at room temperature for 24 h. Methanol (3 ml) was added, and the solution was refluxed for 5 min. The solvent was evaporated *in vacuo*, and the residue was separated by column chromatography with silica gel using ethyl acetate–ethanol (10 : 1) mixture as eluent. Fractions with R_f 0.47 were collected. The solvent was evaporated *in vacuo* to dryness. Yield 133 mg (40%), yellowish powder, mp 130–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49–1.68 (m, 6H, 3CH_2^{azep}), 1.68–1.85 (m, 8H, CH_2^{azep} + + 3$CH_2^{cyclopent}$), 1.85–2.00 (m, 2H, $CH_2^{cyclopent}$), 3.07 (p, 1H, $CH^{cyclopent}$, *J* 9.0 Hz), 3.28 (s, 3H, NMe), 3.33 (s, 3H, NMe), 3.44–3.57 (m, 4H, 2NCH_2^{azep}), 4.72 (s, 1H, CH^{pyrim}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0 (2$CH_2^{cyclopent}$), 26.8 (2CH_2^{azep}), 27.6 (NMe), 28.2 (2CH_2^{azep}), 30.3 (NMe), 31.1 (2$CH_2^{cyclopent}$), 41.8 ($CH^{cyclopent}$), 49.6 (2NCH_2^{azep}), 84.5 (CH^{pyrim}), 152.9 (C=O), 156.4 ($C^{4\ pyrim}$), 163.5 (C=O), 164.2 ($C^{amidine}$). MS (EI), *m*/*z* (%): 332 $[M]^+$ (36), 291 (29), 140 (100), 98 (72), 82 (77), 55 (83). IR (NPVO, ZnSe, ν/cm^{-1}): 1150, 1366, 1417, 1467, 1563, 1585, 1640, 1912, 2866, 2927. Found (%): C, 65.36; H, 8.37; N, 16.80. Calc. for $C_{18}H_{28}N_4O_2$, (%): C, 65.03; H, 8.49; N, 16.85.

§ *1,3-Dimethyl-6-{(*E*)-[(morpholin-4-yl)(oxolan-3-yl)methylidene]amino}pyrimidine-2,4(1*H*,3*H*)-dione* **3g**.

Method A. Azide **1a** (181 mg, 1 mmol) was added to a mixture of morpholine (155 mg, 1.78 mmol), tetrahydropyran-4-one (177 mg, 1.77 mmol) and 1,4-dioxane (2 ml), and this was stirred at room temperature for 24 h. Methanol (3 ml) was added, and the solution was refluxed for 5 min. The solvent was evaporated *in vacuo* and the residue was separated by column chromatography with silica gel using ethyl acetate–ethanol (10 : 1) mixture as eluent. Fractions with R_f 0.21 were collected. The solvent was evaporated *in vacuo* to dryness. Yield 96 mg (30%).

Method B. A mixture of azide **1a** (181 mg, 1 mmol) and enamine **2e** (209 mg, 1.25 mmol) in 1,4-dioxane (2 ml) was stirred at room temperature for 24 h. Then the solution was refluxed for 2 min. The isolation was similar to that in Method A. The product was recrystallized from minimal amount of methanol. Yield 200 mg (62%), colourless powder, mp 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–2.09 (m, 1H, CH^{fur}), 2.15–2.32 (m, 1H, CH^{fur}), 3.24 (s, 3H, NMe), 3.34 (s, 3H, NMe), 3.50–3.60 (m, 1H, OCH^{fur}), 3.60–3.78 (m, 9H, 2NCH_2^{morph} + CH^{fur} + + 2OCH_2^{morph}), 3.83 (t, 1H, OCH^{fur}, *J* 9.7 Hz), 3.89–3.99 (m, 1H, OCH^{fur}), 4.22 (t, 1H, OCH^{fur}, *J* 8.0 Hz), 4.79 (s, 1H, CH^{pyrim}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.8 (NMe), 30.4 (NMe), 32.4 (CH_2^{fur}), 39.3 (CH^{fur}), 46.2 (2NCH_2^{morph}), 66.6 (2OCH_2^{morph}), 69.0 (OCH_2^{fur}), 70.1 (OCH_2^{fur}), 86.4 (CH^{pyrim}), 152.6 (C=O), 156.8 ($C^{4\ pyrim}$), 161.8 ($C^{amidine}$), 163.3 (C=O). MS (EI), *m*/*z* (%): 322 $[M]^+$ (25), 279 (41), 166 (24), 140 (75), 86 (40), 82 (100), 55 (77). IR (NPVO, ZnSe, ν/cm^{-1}): 1261, 1359, 1420, 1570, 1637, 1691, 2846, 2932. Found (%): C, 55.70; H, 6.54; N, 17.63. Calc. for $C_{15}H_{22}N_4O_4$ (%): C, 55.89; H, 6.88; N, 17.38.

¶ *Crystallographic data for* **3g**. Single crystal (colourless prism, 0.44 × 0.38 × 0.31 mm), $C_{15}H_{22}N_4O_4$, monoclinic, space group *C*2/*c*, *a* = 17.777(17), *b* = 9.480(5) and *c* = 18.867(9) Å, β = 99.83(6)°, *V* = = 3133(4) A^3, *Z* = 8. Analysis was performed at 295(2) K on an Xcalibur 3 diffractometer using graphite monochromated MoKα radiation (λ = = 0.71073 Å) and CCD detector. On the angles 4.74 < θ < 65.26, 18795 reflections were collected, among them 2702 were unique (R_{int} = 0.074), 1750 reflections with $I > 2\sigma(I)$. The structure was solved by direct method and refined by full-matrix least squares at F^2 using the SHELXTL program package.[12] All non-hydrogen atoms were refined anisotropically, the positions of the hydrogen atoms were calculated using a riding model in isotropic approximation. GOF at F^2 was 1.00; final *R* values [$I > 2\sigma(I)$]: R_1 = 0.050, wR_2 = 0.121; *R* values (all reflections): R_1 = = 0.0817, wR_2 = 0.1119; largest diff. peak/hole 0.19/–0.20 eÅ^{-3}.

CCDC 1848301 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.

2 S. Donnini, M. Monti, C. Castagnini, R. Solito, M. Botta, S. Schenone, A. Giachetti and M. Ziche, *Int. J. Cancer*, 2007, **120**, 995.
3 (*a*) A. Bazgir, M. M. Khanaposhtani and A. A. Soorki, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5800; (*b*) N. Z. Shaban, M. S. Masoud, M. A. Mawlawi, D. Awad and O. M. Sadek, *J. Physiol. Biochem.*, 2012, **68**, 475.
4 S. Pandey, S. N. Suryawanshi, S. Gupta and V. M. L. Srivastava, *Eur. J. Med. Chem.*, 2004, **39**, 969.
5 (*a*) A. E. G. Amr, S. S. Maigali and M. M. Abdulla, *Monatsh. Chem.*, 2008, **139**, 1409; (*b*) A. E. Amr, A. M. Mohamed, S. F. Mohamed, N. A. Abdel-Hafez and A. G. Hammam, *Bioorg. Med. Chem.*, 2006, **14**, 5481.
6 (*a*) B. J. Branstetter, J. G. Breitenbucher, A. D. Lebsack and W. Xiao, *Patent WO 2008005303 A2*, 2008; (*b*) E. E. Flefel, M. A. Salama, M. El-Shahat, M. A. El-Hashash and A. F. El-Farargy, *Phosphorus Sulfur Silicon Relat. Elem.*, 2007, **182**, 1739; (*c*) E. V. Verbitskiy, S. A. Baskakova, N. A. Gerasimova, N. P. Evstigneeva, N. V. Zil'berberg, N. V. Kungurov, M. A. Kravchenko, G. L. Rusinov, O. N. Chupakhin and V. N. Charushin, *Mendeleev Commun.*, 2018, **28**, 393.
7 (*a*) K. Liubchak, A. Tolmachev, O. O. Grygorenko and K. Nazarenko, *Tetrahedron*, 2012, **68**, 8564; (*b*) M. Shimizu, N. Hayama, T. Kimachi and K. Inamoto, *Synthesis*, 2017, **49**, 4183; (*c*) S. Dudkin, V. O. Iaroshenko, V. Ya. Sosnovskikh, A. A. Tolmachev, A. Villinger and P. Langer, *Org. Biomol. Chem.*, 2013, **11**, 5351; (*d*) L. Saikia, B. Das, P. Bharali and A. J. Thakur, *Tetrahedron Lett.*, 2014, **55**, 1796; (*e*) V. O. Iaroshenko, S. Dudkin, V. Ya. Sosnovskikh, A. Villinger and P. Langer, *Synthesis*, 2013, **45**, 971.
8 (*a*) I. Efimov, N. Beliaev, T. Beryozkina, P. Slepukhin and V. Bakulev, *Tetrahedron Lett.*, 2016, **57**, 1949; (*b*) I. Efimov, V. Bakulev, N. Beliaev, T. Beryozkina, U. Knippschild, J. Leban, Z.-J. Fan, O. Eltsov, P. Slepukhin, M. Ezhikova and W. Dehaen, *Eur. J. Org. Chem.*, 2014, 3684.
9 (*a*) N. A. Beliaev, M. Z. Shafikov, I. V. Efimov, T. V. Beryozkina, G. Lubec, W. Dehaen and V. A. Bakulev, *New J. Chem.*, 2018, **42**, 7049; (*b*) V. A. Bakulev, T. Beryozkina, J. Thomas and W. Dehaen, *Eur. J. Org. Chem.*, 2018, 262; (*c*) V. A. Bakulev, I. V. Efimov, N. A. Belyaev, Yu. A. Rozin, N. N. Volkova and O. S. El'tsov, *Chem. Heterocycl. Compd.*, 2012, **47**, 1593 (*Khim. Geterotsikl. Soedin.*, 2012, 1900).
10 A. A. Anderson, S. P. Symonyan and E. Lucevics, *Chem. Heterocycl. Compd.*, 1998, **34**, 1406 (*Khim. Geterotsikl. Soedin.*, 1998, 1658).
11 S. Pellegrino, A. Contini, M. L. Gelmi, L. L. Presti, R. Soave and E. Erba, *J. Org. Chem.*, 2014, **79**, 3094.
12 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.

Received: 19th June 2018; Com. 18/5613