Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *87* (2) 169–179 (2021)
JSCS–5513
Original scientific paper
Published 1 October 2021

Synthetic route towards 1,2,3,4-tetrahydroquinoxaline/ /piperidine combined tricyclic ring system

MIHAJLO J. KRUNIĆ[#], IVANA I. JEVTIĆ*[#], JELENA Z. PENJIŠEVIĆ[#] and SLAĐANA V. KOSTIĆ-RAJAČIĆ[#]

University of Belgrade-Institute of Chemistry, Technology and Metallurgy, Department of Chemistry, Njegoševa 12, 11000 Belgrade, Serbia

(Received 16 April, revised 2 August, accepted 20 August 2021)

Abstract: The synthetic route toward novel tricyclic, nitrogen-containing system is disclosed. Three novel compounds possessing structural features of 1,2,3,4-tetrahydroquinoxaline and decahydropyrido[3,4-*b*]pyrazine are synthesized starting from readily available precursors in six or seven steps, of which the last three or four steps respectively are diastereoselective. Key reaction steps include *N*-acylation, Hofmann rearrangement and ring-closing Buchwald–Hartwig reaction. Compounds *trans*-**8**, *cis*-**12** and *trans*-**12** are synthesized in order to prove that this novel, tricyclic system can be functionalized with various groups. Synthetic significance of this heterocyclic system lies in the possibility for the orthogonal functionalization of three different amino groups, allowing fine structural tuning.

Keywords: heterocycles; 1,2,3,4-tetrahydroquinoxaline; piperazine; anilidopiperidine; Buchwald–Hartwig reaction.

INTRODUCTION

Nitrogen-containing heterocycles represent very important structural moieties occurring in many pharmacologically active compounds.[1,2] Almost 75 % of all Food and Drug Administration (FDA) approved drugs possess nitrogen heterocycles as pharmacophores.[3]

The possibilities for the derivatization of nitrogen functional groups make these heterocycles significant as intermediates in the organic synthesis. Moreover, nitrogen heterocycles can form versatile noncovalent interactions with the protein target including electrostatic interactions, hydrogen bonding, dipole–dipole interactions, etc., which makes them desirable as pharmacophores in medicinal chemistry.[4] Due to their significance for organic chemistry in general,

* Corresponding author. E-mail: ivana.jevtic@ihtm.bg.ac.rs
[#] Serbian Chemical Society member.
https://doi.org/10.2298/JSC210416068K

the design of new nitrogen heterocycles and the development of new, more efficient ways for their synthesis has been a subject of many research projects, for several decades now.[5]

Both quinoxalines and their derivatives 1,2,3,4-tetrahydroquinoxalines represent an important class of nitrogen-containing heterocycles that can be found in many pharmacologically active natural and synthetic compounds (Fig. 1).[6,7] 1,2,3,4-tetrahydroquinoxalines are structural motifs present in compounds that act as anticancer agents,[8] prostaglandin D2 receptor antagonists,[9] cholesteryl ester transfer protein inhibitors,[10] and others.[11–13]

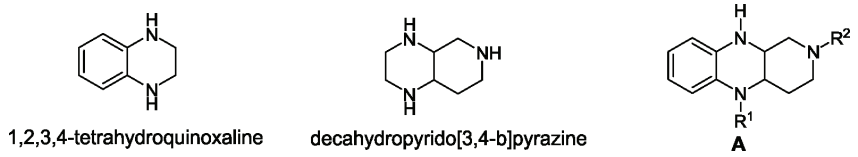


Fig. 1. Structures of the novel tricyclic system of general structure **A** and similar known heterocycles.

Many synthetic procedures for the synthesis of functionalized 1,2,3,4-tetrahydroquinoxalines have been reported so far. Among the most common approaches are the catalytic hydrogenation of quinoxaline,[14–16] and reactions including aniline derivatives such as cyclization/reduction or oxidation/cyclization reactions, including reactions of *o*-phenylenediamines or *o*-nitroanilines,[17] with various ketones,[18,19] dihydroxy compounds[20] or butanedione.[17] Majumdar *et al.* proposed iodocyclization as a method for constructing 1,2,3,4-tetrahydroquinoxalines among the other heterocycles, starting from *o*-substituted aniline derivatives possessing an isolated, unsaturated C–C bond.[21] Tandem reduction/reductive aminations,[22] and reduction/Michael addition,[23] have been reported by Bunce *et al.* to produce functionalized 1,2,3,4-tetrahydroquinoxalines, starting from *o*-nitroaniline. Organometallic catalyzed intramolecular couplings have also been reported. Yang *et al.* reported the synthesis of 1,2,3,4-tetrahydro-2-vinylquinoxalines *via* palladium (II)-catalyzed tandem allylation of *o*-phenylenediamines with *cis*-1,4-diacetoxy-2-butene.[24] Palladium-catalyzed regio- and stereoselective tandem arylation/heteroannulation reaction afforded 2-alkyl(aryl)idenequinoxalines,[25] while intramolecular Buchwald–Hartwig reaction of 2-haloanilines with sulfonamido group has also been reported.[26] Krchnak *et al.* reported tin (II)-catalyzed solid-phase cyclization of functionalized *o*-nitroanilines, via intramolecular nucleophilic substitution.[27] Microwave assistant reductive cyclization of substituted *o*-nitroaniline afforded 1,2,3,4-tetrahydroquinoxalines, as reported by Merisor *et al.*[28] However, limitations in most cases include low yields, complicated reaction procedures and expensive catalysts. Cyclization/acylation of *o*-phenylenediamines with α-chloroketones[29] and diboronic acid

mediated cyclization/cascade transfer hydrogenation of *o*-phenylenediamines and *o*-nitroanilines with 1,2-dicarbonyl compounds,[30] are some recent examples towards more efficient synthesis of 1,2,3,4-tetrahydroquinoxalines.

On the contrary to the well-known 1,2,3,4-tetrahydroquinoxalines, there are only a few reports on decahydropyrido[3,4-*b*]pyrazines (Fig. 1). Those include several indole derivatives investigated for their antihypertensive[31,32] and analgesic[33] activity more than three decades ago, among which the most notable example was the antihypertensive agent atriposin, albeit it was never marketed.

The value of polycyclic nitrogen-containing heterocycles for synthetic and medicinal chemistry has already been disclosed. As a part of our ongoing research on functionalized nitrogen heterocycles, we envisaged the synthesis of general structure **A** possessing 1,2,3,4-tetrahydroquinoxaline and decahydropyrido-[3,4-*b*]pyrazine moieties fused in a novel tricyclic system (Fig. 1). The presence of three secondary amino groups that can be selectively functionalized in different reaction steps, thus allowing the formation of orthogonally protected or highly functionalized derivatives, is a valuable asset in synthetic chemistry. That can be especially important for the synthesis of bifunctional or bidentate ligands in multi-target drug design. The tricyclic system presented in this paper is practically unknown, except for the single lactam structure.[34]

EXPERIMENTAL

General information

Unless stated otherwise all solvents were freshly distilled under argon prior to being used. All reagents that were purchased from a commercial vendor were used as supplied.

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance III spectrometer, at 500 MHz for the proton (^{1}H) and at 126 MHz for the carbon (^{13}C), and Varian/Agilent, at 400 MHz for the proton (^{1}H) and at 101 MHz for the carbon (^{13}C). Chemical shifts are given in ppm from tetramethylsilane (TMS) as internal standard in deuterated chloroform ($CDCl_3$). 2D NMR spectra (HSQC) were recorded at 400 and 500 MHz. Coupling constants (*J*) are rep-.orted in Hz. Unless stated otherwise, all spectra were recorded at 25 °C. High resolution mass spectra (HRMS) were obtained with a heated ESI (HESI)-LTQ Orbitrap XL spectrometer.

All reactions were monitored by thin layer chromatography (TLC). Dry-column flash chromatography was carried out using silica gel (10–18 or 18–32 μm, ICN-Woelm). Melting points were obtained at a heating rate of 4 °C/min, and are uncorrected.

IR spectra were recorded by using a Thermo Scientific Nicolet 6700 Fourier-transform spectrometer operated in the ATR mode.

Structures of all new compounds were determined by methods of 1D, 2D NMR and IR spectroscopy. Structures of the final two compounds were additionally confirmed by high resolution mass spectrometry (HRMS).

Analytical and spectral data of the compounds are given in Supplementary material to this paper.

Syntheses

*General procedure for the synthesis of enamines **3a** and **3b**.*[35] To a magnetically stirred solution of methyl 1-benzyl-4-oxopiperidine-3-carboxylate **1** (20.0 mmol) in acetic acid

(AcOH, 20 ml), 2-bromoaniline **2a** or 2-iodoaniline **2b** (28.0 mmol) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC (SiO_2 plates; petroleum ether/ethyl acetate (EtOAc), 8:2). After 24 h, the mixture was concentrated by rotary evaporator, and then neutralized with 1.5 M solution of Na_2CO_3 (pH ~11). The mixture was extracted with EtOAc (2×50 ml), and collected organic layers were concentrated by rotary evaporator. The product was purified by recrystallization from isopropyl alcohol (*i*-PrOH).

*General procedure for the synthesis of anilinoesters **4a** and **4b***.[35] To a magnetically stirred solution of enamine **3a** or **3b** (9.4 mmol) in methanol (MeOH, 65 ml), $NaBH_3CN$ (13.2 mmol) and AcOH (28.2 mmol) were added and the mixture was stirred at room temperature. The reaction was monitored by TLC (SiO_2 plates; petroleum ether/EtOAc, 8:2). After 24 h, conc. HCl was added to pH ~1, and the mixture was concentrated by rotary evaporator. The mixture was neutralized with 1.5 M solution of Na_2CO_3 (pH ~11) and extracted with EtOAc (3×50 ml). The combined organic layers were concentrated by rotary evaporator providing the crude product (mixture of *cis*- and *trans*-diastereomers). Diastereomers were separated by dry-column flash chromatography (SiO_2; petroleum ether/EtOAc, 10:0 to 7:3) for the spectroscopic analysis; however, the mixture of *cis/trans* diastereomers was used in the next step, without separation.

*General procedure for the synthesis of anilinocarboxamides **5a** and **5b***.[35] To a magnetically stirred solution of anilinoester *cis/trans*-**4a** or *cis/trans*-**4b** (4.4 mmol) in *N*,*N*-dimethylformamide (DMF, 8 ml), LiH (8.8 mmol) and formamide ($HCONH_2$, 17.6 mmol) were added. The mixture was stirred at room temperature. The reaction was monitored by TLC (SiO_2 plates; CH_2Cl_2/MeOH, 95:5). After 24 h, the mixture was concentrated by rotary evaporator and partitioned between water (100 ml) and CH_2Cl_2 (3×30 ml). The combined organic layers were concentrated by rotary evaporator, affording the crude product as a mixture of *cis*- and *trans*-diastereomers. Diastereomers were separated by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH, 100:0 to 95:5) and used in the next step as separate diastereomers.

*General procedure for the synthesis of anilidocarboxamides **9a** and **9b***. To a magnetically stirred solution of anilinocarboxamide **5a** and **5b** (1.1 mmol) in DMF (8 ml), pyridine (3.3 mmol), 4-(dimethylamino)pyridine (DMAP, 0.33 mmol) and propionyl bromide (EtCOBr, 11.0 mmol) were added and the mixture was stirred at room temperature. The reaction was monitored by TLC (SiO_2 plates; CH_2Cl_2/MeOH, 95:5). The mixture was concentrated by rotary evaporator, and a 1.5 M solution of Na_2CO_3 was added (pH ~11). The mixture was extracted with CH_2Cl_2 (3×30 ml), and the combined organic layers were concentrated by rotary evaporator. The product was dissolved in methanolic ammonia (7–9 M, 30 ml) and the mixture was stirred at room temperature. The reaction was monitored by TLC (SiO_2 plates; CH_2Cl_2/MeOH, 95:5). After 24 h, the mixture was concentrated by rotary evaporator and the crude product was purified by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH, 100:0 to 95:5).

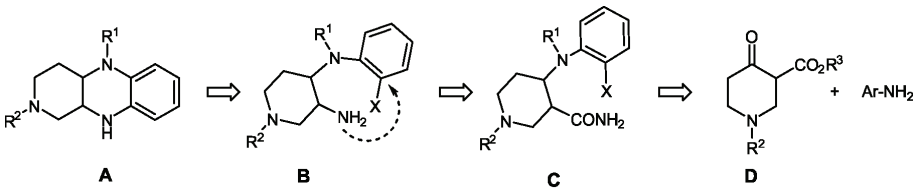
*General procedure for the synthesis of carbamates **6a**, **10a** and **10b***.[36] To a magnetically stirred solution of carboxamide *trans*-**5a**, *trans*-**9a**, *cis*-**9b** or *trans*-**9b** (1.0 mmol) in MeOH (8 ml), $LiOH{\cdot}H_2O$ (8.0 mmol) was added at room temperature. *N*-Bromoacetamide (NBA, 3.0 mmol) was added in three 1mmol aliquots while the mixture was stirred at 60 °C in the dark. The reaction was monitored by TLC (SiO_2 plates; Petroleum ether/EtOAc, 6:4). After 5 min, the mixture was concentrated by rotary evaporator, and mixed with a 1 M solution of NaOH. The mixture was extracted with CH_2Cl_2 (3×30 ml), and the collected organic layers were concentrated by rotary evaporator. The crude product was purified by dry-column flash chromatography (SiO_2; petroleum ether/EtOAc, 10:0 to 6:4).

*General procedure for the synthesis of compounds **7a**, **11a** and **11b**.*[35] To a magnetically stirred solution of carbamate *trans*-**6a**, *trans*-**10a**, *cis*-**10b** or *trans*-**10b** (0.22 mmol) in dichloroethane (2 ml), Me_3SiI (0.77 mmol) was added, and the mixture was stirred at room temperature in the dark. The reaction was monitored by TLC (SiO_2 plates; CH_2Cl_2/MeOH, 95:5). After 24 h, excess of MeOH was added and the mixture was allowed to stir for 15 min. The mixture was then concentrated by rotary evaporator and a 1 M HCl was added in excess, followed by the neutralization with 1.5 M Na_2CO_3. The mixture was extracted with CH_2Cl_2 (3×15 ml) and the combined organic layers were concentrated by rotary evaporator affording the crude product. Crude products were used in the next step without further purification.

*General procedure for the synthesis of compounds trans-**8**, cis-**12** and trans-**12**.* To a magnetically stirred solution of compound *trans*-**7a**, *cis*-**11b** or *trans*-**11a** (0.17 mmol) in 1,4-dioxane (2 ml), *tert*-butyl alkoxide (*t*-BuONa, 0.26 mmol) or Cs_2CO_3 (0.34 mmol) was added. After 5 min, $Pd(OAc)_2$ (0.0034 mmol) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP, 0.01 mmol) were added, and the mixture was stirred at reflux under argon atmosphere. The reaction was monitored by TLC (SiO_2 plates; CH_2Cl_2/MeOH, 95:5). After 8 h, the mixture was concentrated by rotary evaporator. The mixture was partitioned between brine (30 ml) and CH_2Cl_2 (3×10 ml). The combined organic layers were concentrated, and the product was further purified by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH, 100:0 to 95:5).

RESULTS AND DISCUSSION

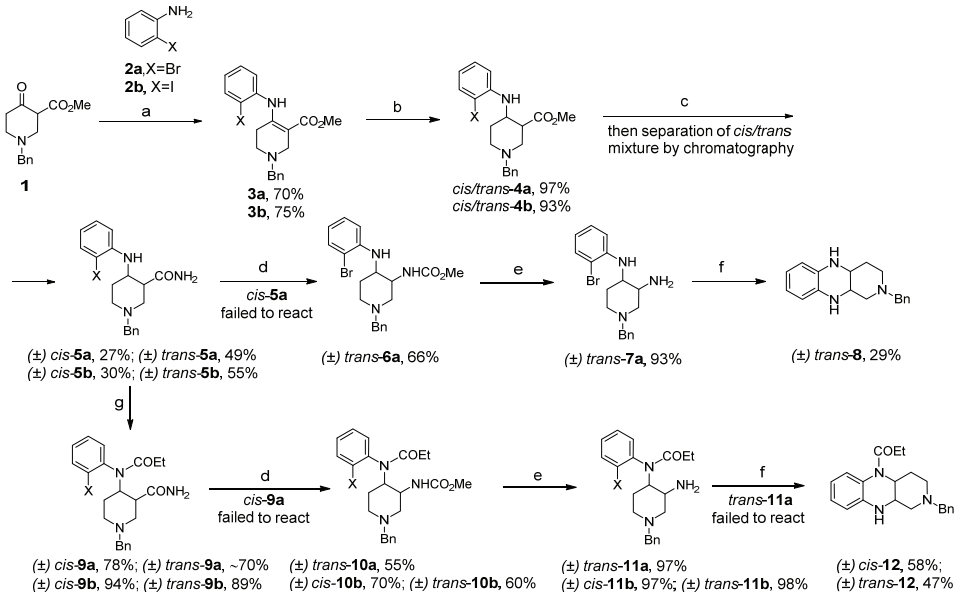
Previously, we disclosed the synthesis of 3-amino-anilidopiperidines, also known as 3-aminofentanyls.[35,36] These compounds are represented by the general structure **B**, where X is hydrogen (Scheme 1). However, we envisaged that the analogues, where X represents bromine or iodine, may provide access to the novel tricyclic system of general structure **A**. The retrosynthetic approach was based on our previously optimized synthesis of 3-aminofentanyls, starting from *β*-ketoester **D** (Scheme 1).[35,36] Therefore, the synthetic protocol was expected to mirror the previous one, except for the use of 2-bromoaniline or 2-iodoaniline that that could possibly influence the reaction conditions and outcomes. The key step, intramolecular Buchwald–Hartwig amination, if successful, would secure the novel heterocyclic system **A,** possessing the combined 1,2,3,4-tetrahydroquinoxaline and decahydropyrido[3,4-*b*]pyrazine moiety.



Scheme 1. The proposed retrosynthetic route to the novel tricyclic system **A**.

The synthetic approach is presented in Scheme 2. The starting *β*-ketoester **1**, while available commercially, was readily prepared on a multi-gram scale, acc. to

our previously published procedure.[37] The *N*-benzyl moiety was chosen since it can be selectively cleaved by various reagents, thus allowing nitrogen functionalization.[38] Condensation of **1** with 2-haloaniline **2a** or **2b** afforded stable enamines **3a** and **b**, respectively, followed by the quantitative reduction to *cis*/*trans* anilinoesters **4a** and **b**. While separable by chromatography, the *cis*/*trans* mixtures were used directly in the next step. In parallel to the earlier results, formamide-mediated aminolysis of the methoxycarbonyl group provided quantitative conversion to carboxamides **5a** and **b**. The procedure typically results in an extensive, base-catalyzed epimerization at C-3,[35] although *cis*/*trans* ratio may vary, depending on the particular diastereomer. The obtained *cis*/*trans* mixtures were quantitatively separated by chromatography or crystallization, furnishing pure *cis*-**5a**, *trans*-**5a**, *cis*-**5b** and *trans*-**5b**. The relative stereochemistry was tentatively assigned *via* 2D NMR spectroscopy only, since no X-ray crystal structures are currently available.



Scheme 2. Reagents and conditions: a) **2a**, **2b**, AcOH, r.t., 24 h; b) $NaBH_3CN$, AcOH, MeOH, r.t., 24 h; c) $HCONH_2$, LiH, DMF, r.t., 16 h; d) NBA, $LiOH{\cdot}H_2O$, MeOH, reflux, 5 min; e) Me_3SiI, $(CH_2)_2Cl_2$, r.t., 24 h; f) $Pd(OAc)_2$, BINAP, *t*-BuONa or Cs_2CO_3, dioxane, reflux, 8 h; g) 1. EtCOBr, pyridine, DMAP, DMF, r.t., 24 h, 2. NH_3/MeOH.

The Hofmann rearrangement was then examined on carboxamides **5a** (Scheme 2). We chose our recently published protocol due to good chemoselectivity and generally high yields, compared to the related methods.[39] As found in the earlier research, the formation of cyclic ureas was expected, via intramolecular addition of aromatic nitrogen to the intermediate isocyanate.

Surprisingly, *trans*-**5a** furnished carbamate *trans*-**6a**. Apparently, the presence of *ortho* bromine precluded cyclization, and the normal carbamate formed instead. However, *cis*-**5a** failed to react analogously, yielding a complex mixture only.

After the removal of the carbamate group and subsequent intramolecular Buchwald–Hartwig reaction of amine *trans*-**7a**, the cyclization product *trans*-**8** was obtained, although in low yields. Compound *trans*-**8** represents essentially a novel class of heterocycles on its own, not readily accessible by alternative approaches. However, since both piperazine nitrogens are unprotected and the selective functionalization is practically not possible, this particular cyclization appears to be of a limited significance. Nonetheless, a potential improvement of the Hofmann rearrangement and the use of aryl iodides instead of bromides could substantially improve the usefulness of the transformation.

To increase the synthetic significance of this cyclization, and the novel heterocyclic system, the protection of one piperazine nitrogen had to be achieved earlier in the synthetic pathway. In our previous research,[35] we found that aromatic amines analogous to **5** (having phenylamino group), were unusually difficult to acylate, likely due to the interference of carboxamido group, rather than the typical steric hindrance. In the case of all four carboxamides **5**, the acylation completely failed with propionyl chloride, under any attempted conditions. Apparently, the presence of *ortho* halogens drastically reduced the nucleophilicity of the aromatic nitrogen. After numerous experiments, it was found that the use of propionyl bromide, in the presence of pyridine and DMAP in DMF, was the only effective reagent for the acylation. Comparable to the previous findings,[35] acyl-amido group formed concomitantly (not shown in the Scheme 2), and then was selectively cleaved by methanolic ammonia. The four obtained carboxamides **9** were used as substrates for the Hofmann rearrangement.[35] Surprisingly, only *trans*-**9a** and *trans*-**9b** reacted as anticipated, providing carbamates *trans*-**10a** and *trans*-**10b** respectively, albeit in modest yields, with high amount of recovered carboxamides. Carboxamides *cis*-**9a** and *cis*-**9b** yielded complex mixtures with no expected carbamates. Upon further examination of the reaction conditions, we discovered that gradual addition of the small amounts of NBA, not only increase the yields of *trans* carbamates, but also it allowed the formation of *cis*-**10b** carbamate from the carboxamide *cis*-**9b**. Presumably, decomposition of NBA under these conditions occurred more rapidly than the reaction with carboxamides. Carboxamide *cis*-**9a** however, yielded complex mixtures with no expected carbamates, under any attempted conditions, similarly as in the case of *cis*-**5a**. We did not further investigate this phenomena, since we had both diastereomers of **10b** to proceed with the next reaction steps. Subsequent removal of the carbamate group using Me_3SiI, furnished amines *trans*-**11a**, *cis*-**11b** and *trans*-**11b**, in nearly quantitative yields. With the required amines at hand, we

were able to examine the intramolecular Buchwald–Hartwig amination, a key transformation of this synthesis. The reaction conditions were mainly chosen from the numerous literature reports, while the phosphine ligand was limited to BINAP, as the only one available.[40] Also, having fairly sensitive substrates, strong bases were to be avoided, with the preference to alkaline earth carbonates. Despite numerous attempts, *trans*-**11a** did not produce the expected product. The use of Cs_2CO_3 in dioxane mainly resulted in the recovered reactant, while in diglyme, at 120–140 °C, it decomposed. The reaction also resulted in the decomposition with *t*-BuONa, probably because it is a much stronger base than alkali metal carbonates. Changing molar ratios of $Pd(OAc)_2$ and BINAP had no significant effect. Fortunately, both diastereomers of **11b**, gave the piperazines *cis*-**12** and *trans*-**12** diastereoselectively, and in moderate yields. The higher yield in the case of *cis*-**12** can be due to the more favorable orientation of the primary amino group and aryl iodide in *cis*-**11b**.

Compounds *cis*-**12** and *trans*-**12** represent another two examples of the novel class of tricyclic, nitrogen-containing system. Obtaining both diastereomers is of significance, since it demonstrates the adaptability of the synthetic route, especially the cyclization process. Also, these heterocycles are suitably functionalized for further elaboration, and as such are potential precursors of pharmacologically active compounds. The piperidine nitrogen, protected by benzyl group, can be readily deprotected and used as a reactive, secondary amino function. One of the piperazine nitrogens is free and can be acylated or alkylated independently, while the other nitrogen is protected as carboxamide.

Thus, we were able to prove that the initial synthetic plan was viable, although, at present, with some limitations. Aryl bromides are apparently insufficiently reactive substrates in these particular aminations, limiting the choice to the iodides. There is a plethora of phosphine ligands, some of which known to be more active than BINAP, permitting additional variations.[26,40] On the other hand, Cs_2CO_3 as a base is effective, with the potential alternatives including K_2CO_3, K_3PO_4, and other reagents less basic than alkoxides. As already mentioned, the formation of 1,2,3,4-tetrahydroquinoxaline core by Buchwald–Hartwig cyclization is known from literature.[26] However, this cyclization is significantly different from ours. The former presents *N*-arylation of a sulfonamido group, whereas in our case, the nucleophile is the primary amino group. From our experience and findings in the literature, the reactivity of amides and amines in Buchwald–Hartwig reaction is different, often requiring very different reaction conditions.

CONCLUSION

The synthetic route toward novel, tricyclic nitrogen containing system is presented herein. Three novel compounds, possessing 1,2,3,4-tetrahydroquinoxaline

and decahydropyrido[3,4-*b*]pyrazine moieties, are synthesized starting from readily available precursors in six or seven steps, of which the last three or four steps respectively, are diastereoselective. Synthetically challenging *N*-acylation of the secondary arylamino group in the presence of adjacent, primary carboxamide function, is optimized. Optimized, NBA-mediated Hofmann rearrangement, gave the desired carbamates in the case of *trans*-**5a** and *trans*-**9a**, *cis*-**9b** and *trans*-**9b**. Carbamate cleavage, followed by the intramolecular Buchwald–Hartwig reaction as the cyclization step, afforded novel tricyclic compounds *trans*-**8**, *cis*-**12** and *trans*-**12** in moderate yields. Such nitrogen containing heterocyclic systems can be of interest for organic synthesis and as building blocks in medicinal chemistry, since the orthogonal functionalization of three different amino groups allows the fine structural tuning. However, an extensive further investigation would be necessary to confirm the potential scope and usefulness of the present results.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/10671, or from the corresponding author on request.

Acknowledgement. The authors would like to thank the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No: 451-03-9/2021-14/ /200026) for financial support.

ИЗВОД

СИНТЕТСКИ ПУТ ЗА ДОБИЈАЊЕ 1,2,3,4-ТЕТРАХИДРОХИНОКСАЛИНСКО/ПИПЕРИДИНСКОГ ТРИЦИКЛИЧНОГ СИСТЕМА

МИХАЈЛО Ј. КРУНИЋ, ИВАНА И. ЈЕВТИЋ, ЈЕЛЕНА З. ПЕЊИШЕВИЋ и СЛАЂАНА В. КОСТИЋ-РАЈАЧИЋ

Универзитет у Београду-Институт за хемију, технологију и металургију, Центар за хемију, Његошева 12, 11000 Београд

У овом раду представљена је синтеза новог трицикличног система који садржи азот. Три нова једињења код којих су комбиноване структурне карактеристике 1,2,3,4-тетрахидрохиноксалина и декахидропиридо[3,4-*b*]пиразина, добијена су полазећи од лако доступних прекурсора, у шест или седам фаза од којих су последње три или четири, редом, диастереоселективне. Кључне синтетичке трансформације укључују *N*-ацилование, Hofmann премештање и интрамолекулску Buchwald–Hartwig реакцију, као фазу у којој долази до циклизације. Једињења *trans*-**8**, *cis*-**12** и *trans*-**12** су синтетисана како би се представила могућност функционализације новог трицикличног система. Синтетички значај новог хетероцикличног система представљен је у могућности ортогоналне функционализације три различите амино групе, чиме се може постићи фино подешавање структуре.

(Примљено 16. априла, ревидирано 2. августа, прихваћено 20. августа 2021)

REFERENCES

1. B. Zhang, A. Studer, *Chem. Soc. Rev.* **44** (2015) 3505 (https://doi.org/10.1039/C5CS00083A)

2. T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles: Structure, Reations, Syntheses, and Applications*, Wiley-VCH Verlag GmbH & Co.,Weinheim, 2003 (https://doi.org/ 10.1002/352760183X)
3. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem*. **57** (2014) 10257 (https://doi.org/10.1021/jm501100b)
4. N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu, S. B. Jonnalagadda, *Molecules* **25** (2020) 1909 (https://doi.org/10.3390/molecules25081909)
5. S. Sabir, M. I. Alhazza, A. A. Ibrahim, *Catal. Sustain. Energy* **2** (2015) 99 (https://doi.org/10.1515/cse-2015-0009)
6. S. Tariq, K. Somakala, M. Amir, *Eur. J. Med. Chem.* **143** (2018) 542 (https://doi.org/10.1016/j.ejmech.2017.11.064)
7. V. A. Mamedov, N. A. Zhukova, *Prog. Heterocyc. Chem.* **24** (2012) 55 (https://doi.org/10.1016/B978-0-08-096807-0.00002-6)
8. R. Veligeti1, R. B. Madhu, J. Anireddy,V. R. Pasupuleti, V. K. R. Avula, K. S. Ethiraj, S. Uppalanchi, S. Kasturi1, Y. Perumal, H. S. Anantaraju, N. Polkam, M. R. Guda, S. Vallela, G. Vasilievich Zyryanov, *Sci. Rep.* **10** (2020) 20720 (https://doi.org/10.1038/s41598-020-77590-1)
9. K. Torisu, K. Kobayashi, M. Iwahashi, Y. Nakai, T. Onoda, T. Nagase, I. Sugimoto, Y. Okada, R. Matsumoto, F. Nanbu, S. Ohuchida, H. Nakao, M. Toda, *Bioorg. Med. Chem.* **12** (2004) 5361 (https://doi.org/10.1016/j.bmc.2004.07.048)
10. C. T. Eary, Z. S. Jones, R. D. Groneberg, L. E. Burgess, D. A. Mareska, M. D. Drew, J. F. Blake, E. R. Laird, D. Balachari, M. O'Sullivan, A. Allen, V. Marsh, *Bioorg. Med. Chem. Lett.* **17** (2007) 2608 (https://doi.org/10.1016/j.bmcl.2007.01.112)
11. J. J. Chen, W. Qian, K. Biswas, V. N. Viswanadhan, B. C. Askew, S. Hitchcock, R. W. Hungate, L. Arik, E. Johnson, *Bioorg. Med. Chem. Lett.* **18** (2008) 4477 (https://doi.org/10.1016/j.bmcl.2008.07.055)
12. G. Morissette, J. P. Fortin, S. Otis, J. Bouthillier, F. Marceau, *J. Pharmacol. Exp. Ther.* **311** (2004) 1121 (https://doi.org/10.1124/jpet.104.071266)
13. Y. Ohtake, A. Naito, H. Hasegawa, K. Kawano, D. Morizono, M. Taniguchi, Y. Tanaka, H. Matsukawa, K. Naito, T. Oguma, Y. Ezure, Y. Tsuriya, *Bioorg. Med. Chem.* **7** (1999) 1247 (https://doi.org/10.1016/S0968-0896(99)00049-8)
14. A. Patti, S. Pedotti, *Tetrahedron* **66** (2010) 5607 (https://doi.org/10.1016/j.tet.2010.05.090)
15. R. Rahi, M. Fang, A. Ahmed, R. A. Sánchez-Delgado, *Dalton. Trans.* **41** (2012) 14490 (https://doi.org/10.1039/C2DT31533E)
16. W. Tang, L. Xu, Q. H. Fan, J. Wang, B. Fan, Z. Zhou, K. H. Lam, A.S.C. Chan, *Angew. Chem. Int. Ed.* **48** (2009) 9135 (https://doi.org/10.1002/anie.200904518)
17. B. B. F. Mirjalili, A. Akbari, *Chin. Chem. Lett.* **22** (2011) 753 (https://doi.org/10.1016/j.cclet.2010.12.016)
18. C. S. Cho, W. X. Ren, S. C. Shim, *Tetrahedron Lett.* **48** (2007) 4665 (https://doi.org/10.1016/j.tetlet.2007.05.044)
19. F. Pan, T. M. Chen, J. J. Cao, J. P. Zou, W. Zhang, *Tetrahedron Lett.* **53** (2012) 2508 (https://doi.org/10.1016/j.tetlet.2012.02.113)
20. M. J. Climent, A. Corma, J. C. Hernández, A. B. Hungría, S. Iborra, S. Martínez-Silvestre, *J. Catal.* **292** (2012) 118 (https://doi.org/10.1016/j.jcat.2012.05.002)
21. K. C. Majumdar, K. Ray, S. Ponra, *Tetrahedron Lett.* **51** (2010) 5437 (https://doi.org/10.1016/j.tetlet.2010.08.016)

22. R. A. Bunce, D. M. Herron, L. Y. Hale, *J. Heterocycl. Chem.* **40** (2003) 1031 (https://doi.org/10.1002/jhet.5570400611)
23. R. A. Bunce, D. M. Herron, M. L. Ackerman, *J. Org. Chem.* **65** (2000) 2847 (https://doi.org/10.1021/jo991899+)
24. S.-C. Yang, P.-C. Liu, W.-H. Feng, *Tetrahedron Lett.* **45** (2004) 4951 (https://doi.org/10.1016/j.tetlet.2004.04.140)
25. R. Mukhopadhyay, N. G. Kundu, *Synlett* (2001) 1143 (https:/doi.org/10.1055/s-2001-15135)
26. M. K. Ghorai, A. K. Sahoo, S. Kumar, *Org. Lett*. **13** (2011) 5972 (https://doi.org/10.1021/ol2023906)
27. V. Krchnak, J. Smith, J. Vagner, *Tetrahedron Lett.* **42** (2001) 2443 (https://doi.org/10.1016/S0040-4039(01)00197-6)
28. E. Merişor, J. Conrad, I. Klaiber, S. Mika, U. Beifuss, *Angew. Chem. Int. Ed.* **46** (2007) 3353 (https://doi.org/10.1002/anie.200605260)
29. Y. Fu, J. Y. Wang, W. G. Chen, Y. Li, L. X. Zhao, S. Gao, F. Ye, *Heterocycl. Chem.* **54** (2017) 3023 (https://doi.org/10.1002/jhet.2911)
30. S. Liu, Y. Zhou, Y. Sui, H. Liu, H. Zhou, *Org. Chem. Front.* **4** (2017) 2175 (https://doi.org/10.1039/C7QO00604G)
31. G. Oshiro, A. Wojdan, M. Klein, G. Metcalf, *J. Cardiovasc. Pharmacol*. **10** (1987) 341 (https://doi.org./ 10.1097/00005344-198709000-00014)
32. I. Jirkovsky, G. Santroch, R. Baudy, G. Oshiro, *J. Med. Chem.* **30** (1987) 388 (https://doi.org/10.1021/jm00385a022)
33. A. Nurgiin, C. François, (Sanofi Aventis France) EP0287468A2 (1988)
34. M. Królikiewicz, K. Błaziak, W. Danikiewicz, Z. Wróbel, *Synlett* **24** (2013) 1945 (https://doi.org/10.1055/s-0033-1339467)
35. I. I. Jevtić, Lj. Došen-Mićović, E. R. Ivanović, N. M. Todorović, M. D. Ivanović, *Synthesis* **49** (2017) 3126 (https://doi.org/ 10.1055/s-0036-1588985)
36. I. I. Jevtić, K. Savić Vujović, D. Srebro, S. Vučković, M. D. Ivanović, S. V. Kostić-Rajačić, *Pharmacol. Rep*. **72** (2020) 1069 (https://doi.org/ 10.1007/s43440-020-00121-2)
37. J. Popović-Djordjević, S. Stepanović, Lj. Došen-Mićović, E. Ivanović, M. D. Ivanović, *Green Chem. Lett. Rev.* **9** (2016) 61 (https://doi.org/ 10.1080/17518253.2016.1145744)
38. P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis,* 5th ed., John Wiley & Sons, Inc., Hoboken, NJ, 2014, pp. 895–4045 (https://doi.org/10.1002/9781118905074)
39. I. I. Jevtić, Lj. Došen-Mićović, E. R. Ivanović, M. D. Ivanović. *Synthesis* **48** (2016) 1550 (https://doi.org/ 10.1055/s-0035-1561405)
40. R. Dorel, C. P. Grugel, A. M. Haydl, *Angew. Chem. Int. Ed.* **58** (2019) 17118 (https://doi.org/10.1002/anie.201904795).