Tetrahedron Letters 60 (2019) 151089

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cascade reactions for constructing heterocycles containing a pyrimidino-pyrazino-pyrimidine core using 1,2,4-triazole scaffolds

Dmytro M. Khomenko [a,d,*], Roman O. Doroshchuk [a,d], Ilona V. Raspertova [a], Jesús García López [b], Fernando López Ortiz [b], Sergiu Shova [c], Oleg A. Iegorov [d], Rostyslav D. Lampeka [a]

[a] Department of Chemistry, Kyiv National Taras Shevchenko University, Volodymyrska St. 64, Kyiv 01601, Ukraine
[b] Área de Química Orgánica, Research Centre CIAIMBITAL, Universidad de Almería, Ctra. Sacramento s/n, 04120 Almería, Spain
[c] Institute of Chemistry, Academy of Sciences of Moldova, Academiei Str. 3, Chisinău 2028, Republic of Moldova
[d] Enamine Ltd, Vul. Oleksandra Matrosova 23, Kyiv 01103, Ukraine

ARTICLE INFO

Article history:
Received 15 June 2019
Revised 23 August 2019
Accepted 28 August 2019
Available online 28 August 2019

Keywords:
1,2,4-Triazole
Cyclization
Pyrazine
Conformationally rigid

ABSTRACT

The regioselective cyclocondensation of aminoethyl-1,2,4-triazoles and glyoxal provides pentacyclic heterocycles in which two 7,8-dihydro-5*H*-6λ^2-[1,2,4]triazolo[1,5-*c*]pyrimidine systems are connected through CH(OH) bridges generating a central piperazine-2,5-diol ring. The structure of the new compounds was elucidated based on ^{1}H, ^{13}C and ^{15}N NMR spectroscopic methods. The molecular structure of the parent compound generated from aminoethyl-1,2,4-triazole was established by single crystal X-ray diffraction.

Introduction

The chemistry of polycyclic systems containing saturated heterocyclic moieties is one of the most important and flourishing areas in synthetic organic chemistry [1,2]. This is due to the presence of sp^3-hybridized atoms in saturated compounds which make possible the construction of small molecules with semi-rigid frameworks and therefore the introduction of functional groups responsible for molecular recognition into specific positions of the heterocyclic skeleton. This strategy has been called stereochemical diversity oriented restriction [3]. The driving force for this approach is the "lock and key" model [4]. Recently, we have reported the synthesis of mixed unsaturated-saturated condensed heterocycles of the hexahydropyrazino[2,3-*e*]pyrazine family through the reaction between 3-aminomethyl-1,2,4-triazoles and glyoxal [5]. The dialdehyde glyoxal is a widely used constituent for the preparation of saturated heterocycles. For example, the condensation with linear polyamines, *o*-aminophenol or aminoethanol leads to pyrazino-pyrazines [6], 2,2′-bioxazolidines [7] or oxazino-oxazines [8], respectively. Typically, these bicyclic compounds provide the rigid *cis*-fused products due to a stabilizing double anomeric effect [9]. The condensation of glyoxal with benzylamine is the key step in the preparation of the nitroamine explosive 2,4,6,8,10,12-hexanitrohexaazaisowurtzitane (HNIW), also known as CL-20 [10].

Although aminoalkyl-1,2,4-triazoles and their analogues are attractive polyfunctional systems, their synthetic applications remain largely unexplored. Only a few examples of their reactivity towards carbonyl compounds have been reported [11]. They have been used as building blocks for the construction of peptidomimetics *via* acylation of the primary amino group [12], whereas the condensation with aromatic aldehydes and ketones gives rise to [1,2,4]triazolo[1,5-*c*]pyrimidines in moderate to high yield [13]. Interestingly, 3-amino-5-aminoethyl-4*H*-1,2,4-triazoles undergo cyclocondensation with 1,3-dicarbonyl reagents in the presence of HCl exclusively through the 2-amino group affording 2-aminoalkyl-1,2,4-triazolo[1,5-*a*]pyrimidine hydrochlorides [14].

As part of our work on the chemistry of aminoalkyl-1,2,4-triazoles, we report herein the synthesis of three new pentacyclic "pyrazino-pyrimidines" from aminoethyl-1,2,4-triazoles. Compared with the analogous reaction of aminomethyl-1,2,4-triazoles [5], the increase of the alkyl chain length connecting the heterocycle and the amino group led to the formation of a completely different heterocyclic system.

* Corresponding author at: Department of Chemistry, Kyiv National Taras Shevchenko University, Volodymyrska St. 64, Kyiv 01601, Ukraine.
E-mail addresses: dkhomenko@ukr.net (D.M. Khomenko), flortiz@ual.es (F. López Ortiz).

https://doi.org/10.1016/j.tetlet.2019.151089
0040-4039/

Results and discussion

The synthesis of the new heterocyclic system was based on the use 3-aminoethyl-1,2,4-triazoles **6** as building blocks. These precursors were readily accessible starting from commercially available Boc-β-alanine **1** following a slightly modified procedure previously reported for the preparation of aminomethyl-1,2,4-triazoles (Scheme 1) [5]. Thus, transformation of the carboxylic group of **1** into a 1,2,4-triazole moiety was achieved through the formation of ethyl ester **2** followed by conversion into hydrazide **3** and subsequent cyclization by reaction with the corresponding ethyl imidate hydrochloride **4**. Finally, *N*-Boc deprotection using HCl in EtOH-H_2O at reflux afforded the required 3-aminoethyl-1,2,4-triazoles **6a-d** as hydrochlorides. Treating **6a-d** with glyoxal in a water-ethanol solution (1:1 molar ratio) in the presence of Et_3N afforded pyrazino-pyrimidines **7a-d** in high yields as a single stereoisomer. Compounds **7a,c,d** were obtained with a purity higher than 97% (determined by ^{1}H NMR) by simple filtration of the crude reaction mixture. However, **7b** was isolated as a mixture with by-product **8** in a 70:30 ratio. The extremely low solubility of this mixture in all common solvents made its purification by recrystallization or chromatographic methods impossible. Attempts to improve the yield of **7b** using different reaction conditions (time, temperature, and stoichiometry) were unsuccessful.

The formation of the title compounds can be explained by a mechanism of cascade reactions (Scheme 2) involving condensation of aminotriazole **6** with one carbonyl group of glyoxal to give azomethine intermediate **I** which would undergo cyclization through intramolecular attack of the NH group of the 1,2,4-triazole to the C=N moiety furnishing tetrahydro-[1,2,4]triazolo[1,5-*c*] pyrimidine-5-carbaldehyde derivative **II**. Subsequent double hemiaminal formation *via* stepwise intermolecular-intramolecular addition processes between the amino and formyl groups of two molecules of **II** would provide product **7**.

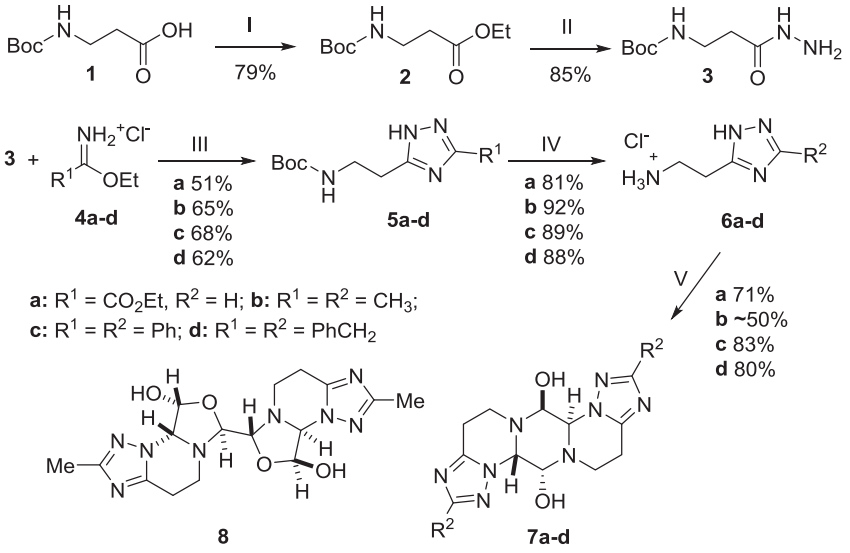
The stereoselective formation of **7** *via* intermediate **II** is supported by computations at the M06-2X/6-31G(d) level of theory (Fig. S16). The conformer of minimum energy **IIa** has the carbonyl group in an equatorial position of the six-membered ring and eclipsed with the NH linkage. This arrangement is stabilized by an intramolecular O···H—N hydrogen bond and would be retained in the reaction with a second molecule of **IIa** through the formation of an intermolecular O···H—N hydrogen bonding leading to **7**.

Alternatively, the successive addition of two molecules of **II** to one molecule of glyoxal would afford intermediate **III**, which is stabilized as the cyclic bis-hemiacetal **8**. The presence of small amounts of other stereoisomers below the detection level of ^{1}H NMR spectra (600 MHz, cryoprobe), could not be discarded due to the extremely low solubility of compounds **7** and **8**.

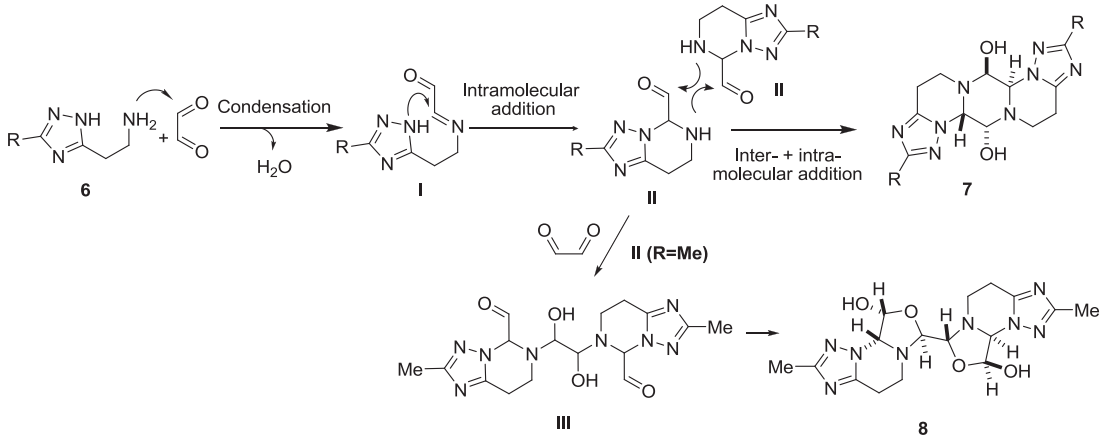
Compound **7a**, which crystalizes in the *P*21/*c* space group of the monoclinic system with two co-crystallized water molecules, was characterized using single-crystal X-ray diffraction analysis [15–17]. The structure is shown in Fig. 1 and the bond distances and angles are summarized in Table S1. Compound **7a** contains an inversion center. The primed atoms are symmetry related by inversion to the unprimed atoms. The central hexahydropyrazine ring has a chair conformation, while the tetrahydropyrimidine rings have a twist-conformation. The deviation of N(1) from the mean plane of atoms C(5)N(2)C(4)C(3)C(2) is −0.26 Å. Two hydroxy groups are in the *trans*-position relative to each other and have an axial orientation to the central ring (torsion angle C(5)N(1)C(1)O(1) −59,15(14)°).

In the crystal, compound **7a** and solvate molecules interact through numerous O—H···N and O—H···O intermolecular hydrogen bonds (Table S2) to form a three-dimensional supramolecular network, as shown in Fig. S2.

The formation of compounds **7** was further supported by MS spectrometry and NMR spectroscopy. Although the solubility of these compounds in deuterated solvents was very low, ^{1}H, ^{13}C and ^{15}N NMR spectra could be acquired for all of them. The NMR spectra show only half the expected number of signals which was in agreement with a structure of C_i symmetry. Using compound **7a** as a reference for structural analysis, the OH signal (H11) at δ 5.75 ppm was established by the lack of correlation in the ^{1}H,^{13}C HSQC spectrum. Protons H6, H10′ (Fig. 1, overlapped



Scheme 1. *Reagents and conditions:* (I) ethyl chloroformate, CH_2Cl_2, 0 °C, 1 h; DMAP, room temp., 12 h. (II) N_2H_4, EtOH, reflux, 10 h. (III) NEt_3, EtOH, reflux, 12 h. (IV) HCl, EtOH-H_2O, reflux, 12 h. (V) Glyoxal, NEt_3, EtOH-H_2O, room temp., 12 h.



Scheme 2. Suggested reaction mechanism for the formation of **7** and **8**.

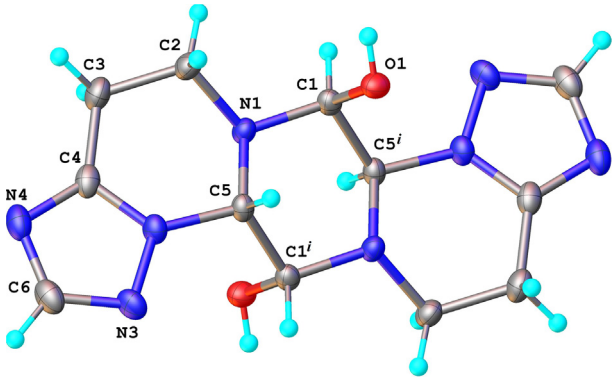


Fig. 1. X-ray molecular structure of **7a** with atom labeling and thermal ellipsoids at 50% probability. Symmetry code: $-x$, $1-y$, $1-z$.

at δ 5.11 ppm) and H11 give rise to an ABX spin system. The correlations observed in the $^{1}H,^{15}N$ HMQC spectrum support the formation of the piperazine-2,5-diol substructure. Thus, protons H9 (δ 2.89 ppm) and H6/H10 (δ 5.11 ppm) correlate with nitrogen atom N7 (δ 55.7 ppm, Fig. 2a). Additionally, H9 shows a second correlation with N2 at δ 208.6 ppm. Finally, N1 (δ 279.6 ppm) and N4 (δ 224 ppm) were identified through their correlations with H5. The ^{15}N chemical shifts of N1, N2 and N4 are in the expected range for 1,2,4-triazoles [18].

A similar NMR study allowed the structure of compound **8** to be determined (Fig. 2). A distinctive feature of **8** is the autocorrelation observed in the HMBC spectrum between H12 and C12′. The relative configuration of C12/C12′ was tentatively assigned based on the absence of NOEs between H12/H12′and nearby protons.

Compounds **7** are the first examples of polyazacycloalkanes containing a dodecahydropyrimido[1′,2′:4,5]pyrazino[1,2-*a*]pyrimidine central core, i.e. a linear arrangement or perhydroanthracene-like skeleton. It has been reported that the condensation of pyridoxamine with glyoxal furnished five-membered ring adducts containing a piperazine-oxazine central system built up by reaction between the amino and phenolic groups of two pyridoxamine with two molecules of glyoxal [19]. Similar geometrical constraints (the O···N distance in pyridoxamine is very close to the $N_{amin}\cdot\cdot N_{trz}$ distance in 3-aminoethyl-1,2,4-triazole) and the acidity of the triazolic and phenolic protons would explain why the reactions of 3-aminoethyl-1,2,4-triazole and pyridoxamine with glyoxal proceed in a similar manner. We have previously observed similar behavior between 3-aminomethyl-1,2,4-triazole and *o*-aminophenol [5]. On the other hand, the analogous perhydrophenanthrene-like or angular bis-aminals (dodecahydropyrimido[2′,1′:3,4]pyrazino[1,2-*a*]pyrimidine) have been prepared by the condensation of glyoxal with linear polyamines [6a,20]. These multidonor systems were used as ligands in coordination chemistry [21]. It is also interesting to note that compound **8** obtained as a by-product in the synthesis of **7b** contains an unprecedented [7,7′-bioxazolo[3,4-*a*][1,2,4]triazolo[1,5-*c*]pyrimidine] structure. The compounds reported herein contain a number of donor atoms of different natures arranged in a rigid heterocyclic core that could be useful for constructing MOF systems, among other applications. We are currently exploring methodologies to achieve that goal.

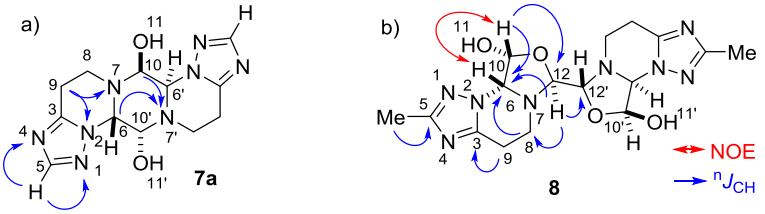


Fig. 2. (a) Correlations observed in the $^{1}H,^{15}N$ HMQC spectrum (blue arrows) of **7a** measured in DMSO d_6 and optimized for a coupling constant of 10 Hz, 1024 scans per increment. Numbering scheme is included. (b) Structure of compound **8** showing key correlations observed in the HMBC spectrum (blue arrows) and the NOE detected between H6 and H10 (red arrow).

Appendix A. Supplementary data

Supplementary data (synthetic procedures, X-ray crystallographic details and copies of spectral data of all new compounds) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151089.

References

[1] A.F. Pozharskii, A.T. Soldatenkov, A.R. Katritzky, Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications, 2nd ed., John Wiley & Sons, Ltd., Chichester, UK, 2011.
[2] C.M. Marson, Adv. Heterocycl. Chem. 121 (2017) 13–33.
[3] C.G. Wermuth, D. Aldous, P. Raboisson, D. Rognan (Eds.), The Practice of Medicinal Chemistry, 4th ed., Academic Press, London, UK, 2015.
[4] J.M. Berg, J.L. Tymoczko, L. Stryer, Biochemistry, 7th ed., International edition., W.H. Freeman and Company, New York, 2012.
[5] D.M. Khomenko, R.O. Doroschuk, V.V. Trachevskii, S. Shova, R.D. Lampeka, Tetrahedron Lett. 57 (2016) 990–992.
[6] (a) F. Chuburu, R. Tripier, M. Le Baccon, H. Handel, Eur. J. Org. Chem. (2003) 1050–1055;
(b) G. Claudon, N. Le Bris, H. Bernard, H. Handel, Eur. J. Org. Chem. (2004) 5027–5030;
(c) M. Argese, M. Brocchetta, M. De Miranda, P. Paoli, F. Perego, P. Rossi, Tetrahedron 62 (2006) 6855–6861;
(d) M. Argese, M. Brocchetta, M. De Miranda, A. Ferraris, P. Dapporto, P. Paoli, P. Rossi, Tetrahedron 63 (2007) 6915–6923;
(e) A. Prokhorov, H. Bernard, N. Le Bris, N. Marquet, H. Handel, Synth. Commun. 38 (2008) 1589–1600;
(f) P. Désogère, C. Bernhard, C. Goze, M.-J. Penouilh, Y. Rousselin, F. Denat, Eur. J. Org. Chem. (2013) 1538–1545.
[7] (a) E. Tauer, K.H. Grellmann, J. Org. Chem. 46 (1981) 4252–4258;
(b) N. Farfán, R. Santillan, J. Guzmán, B. Castillo, A. Ortiz, Tetrahedron 50 (1994) 9951–9960;
(c) A. Ortiz, J. Carrasco, H. Höpfl, R. Santillan, N. Farfán, Synth. Commun. 28 (1998) 1293–1297;
(d) A. Ortiz, N. Farfán, H. Höpfl, R. Santillan, M.E. Ochoa, A. Gutiérrez, Tetrahedron: Asymmetry 10 (1999) 799–811.
[8] (a) B. Alcaide, S. García-Blanco, M.T. García-González, S. Martínez-Carrera, R. Pérez-Ossorio, J. Plumet, I.M. Rodríguez-Campos, Tetrahedron Lett. 27 (1986) 4217–4218;
(b) N. Farfán, R.L. Santillán, D. Castillo, R. Cruz, P. Joseph-Nathan, Can. J. Chem. 70 (1992) 2764–2770;
(c) A. Ortiz, N. Farfán, R. Santillán, M. De Jesús-Rosales, E. García-Báez, J.C. Daran, S. Halut, Tetrahedron: Asymmetry 6 (1995) 2715–2722;
(d) V. Santes, E. Gómez, G. Jiménez, R. Santillan, A. Gutiérrez, N. Farfán, Synth. Commun. 30 (2000) 2721–2734;
(e) M.E. Ochoa, S. Rojas-Lima, H. Höpfl, P. Rodríguez, D. Castillo, N. Farfán, R. Santillán, Tetrahedron 57 (2001) 55–64;
(f) V. Santes, E. Gómez, V. Zarate, R. Santillán, N. Farfán, S. Rojas-Lima, Tetrahedron: Asymmetry 12 (2001) 241–247;
(g) A. Gualandi, F. Manoni, M. Monari, D. Savoia, Tetrahedron 66 (2010) 715–720.
[9] (a) J.E.J. Baldwin, J. Chem. Soc., Chem. Commun. (1976) 734–736;
(b) E. Juaristi, G. Cuevas, Tetrahedron 48 (1992) 5019–5087.
[10] (a) M.R. Crampton, J. Hamid, R. Miller, G. Ferguson, J. Chem. Soc., Perkin Trans. 2 (1993) 923–929;
(b) T.M. Klapötke, B. Krumm, H. Piotrowski, K. Polborn, G. Holl, Chem. Eur. J. 3 (2003) 687–694;
(c) G. Lin, H.-J. Tsai, Y.-H. Tsai, Bioorg. Med. Chem. Lett. 13 (2003) 2887–2890;
(d) G. Herve, G. Jacob, R. Gallo, Chem. Eur. J. 12 (2006) 3339–3344;
(e) T. Kerscher, T.M. Klapötke, B. Krumm, K. Polborn, M. Scherr, J. Fluorine Chem. 127 (2006) 1030–1035;
(f) A.P. Koskin, I.L. Simakova, V.N. Parmon, Russ. Chem. Bull. Int. Ed. 56 (2007) 2370–2375.
[11] A.N. Gusev, V.F. Schul'gin, O.V. Konnic, S.B. Meshkova, G.G. Aleksandrov, M.A. Kiskin, L.I. Eremenko, W. Linert, Inorg. Chim. Acta 376 (2011) 509–514.
[12] J. Cesar, M. Sollner, Synth. Commun. 30 (2000) 4147–4158.
[13] M. Pohl, U. Bechestein, M. Pätzel, J. Liebscher, P.G. Jones, J. Prakt. Chem. 334 (1992) 630–636.
[14] M.A. Prezent, E.D. Daeva, S.V. Baranin, I.V. Zavarzin, Mendeleev Commun. 27 (2017) 169–171.
[15] CrysAlisRED, Oxford Diffraction Ltd., Version 1.171.34.76, 2003.
[16] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H.J. Puschmann, Appl. Cryst. 42 (2009) 339–341.
[17] G.M. Sheldrick, SHELXS, Acta Crystallogr. A64 (2008) 112–122.
[18] (a) A.M. Orendt, J. Michl, J. Reiter, Magn. Reson. Chem. 27 (1989) 1–3;
(b) E. Bednarek, B. Modzelewska-Banachiewicz, M.K. Cyrański, J. Sitkowski, I. Wawer, J. Mol. Struct. 562 (2001) 167–175;
(c) A. Tam, I.S. Armstrong, T.E. La Cruz, Org. Lett. 15 (2013) 3586–3589;
(d) I. Lakomska, M. Babinska, A. Wojtczak, A. Kozakiewicz, J. Sitkowski, A.A. Jarzecki, New J. Chem. 41 (2017) 7775–7782.
[19] (a) P.A. Vozian, T.O. Metz, J.W. Baynes, B.G. Hudson, J. Biol. Chem. 277 (2002) 3397–3403;
(b) M. Colzani, D. De Maddis, G. Casali, M. Carini, G. Vistoli, G. Aldini, ChemMedChem 11 (2016) 1778–1789.
[20] J. Jazwinski, R.A. Kolinski, Tetrahedron Lett. 22 (1981) 1711–1714.
[21] G. Herve, N. Le Bris, H. Bernard, J.-J. Yaouanc, H. Des Abbayes, H. Handel, J. Organomet. Chem. 585 (1999) 259–265.