HETEROCYCLES, Vol. 104, No. 4, 2022, pp. 751 - 763. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 10th December, 2021, Accepted, 11th January, 2022, Published online, 19th January, 2022
DOI: 10.3987/COM-21-14612

ALICYCLIC ANNULATED TRIAZOLES VERSUS TRIAZINEDIONES BY THE REACTION OF CYCLIC IMIDATES WITH METHYL 2-HYDRAZINYL-2-OXOACETATE

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Abstract – A simple convenient method for synthesis of esters of annulated triazole-3-carboxylic acids and/or 1,2,4-triazine-5,6-dione derivatives was proposed. Heating cyclic imidates with methyl 2-hydrazinyl-2-oxoacetate afforded either the annulated triazoles or the annulated triazinediones depending on the reaction conditions. Under heating at hydrochloric acid 1,2,4-triazine-5,6-diones were transformed into triazoles.

INTRODUCTION

Over the past decades, fragment-based drug discovery (FBDD) has proved to be a highly successful method in the search for new candidates for generating new chemical leads and drugs.[1–4] Despite commercial availability of many fragment-like molecules, there is an urgent need to develop and synthesize more new fragments that have small size and apparent simplicity. Recently Rees et al. identified the basic principles that should be considered when designing fragments with optimal chemical properties for FBDD.[5] Two of them can be singled out that relate directly to the structure of the molecule: a) the presence of polar groups capable of performing key interactions with a biological target (lead-like properties) and b) the increase in their degree of saturation i.e. “three-dimensionality”.[6] These principles can be implemented in partially saturated bicyclic heteroaromatic compounds (PSBH), which combine the well-proven lead-like properties of hydrophilic aromatic heterocycles and the "three-dimensional" nature of their saturated analogs.[7–11] Examples of such scaffolds are alicyclic annulated triazoles. These bicyclic systems are embedded in the structure of many bioactive compounds. A few examples are given in Figure 1. Sitagliptin **I** is a hypoglycemic drug used to treat type 2 diabetes mellitus.[12] Compound **II** belongs to γ-secretase modulators as a potential therapeutic agent for treatment of Alzheimer's disease.[13,14] Annulated triazole **III**

demonstrates excellent selectivity towards the key metabolizing enzyme - 15-hydroxyprostaglandin dehydrogenase (15-PGDH).[15] Bicyclic triazole **IV** is a part of the structure of biologically active compounds that are regulators of ASK 1 (Figure 1).[16–18]

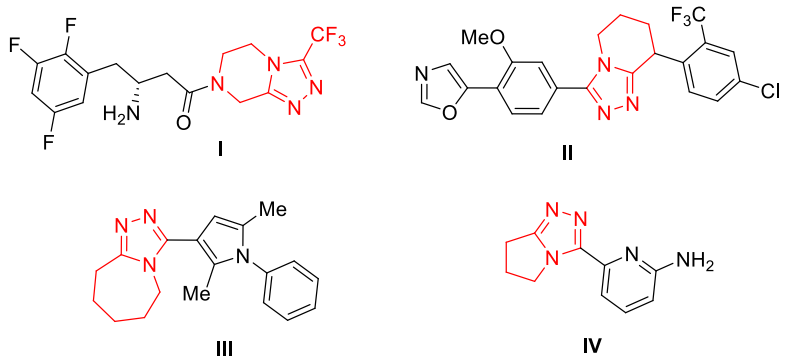


Figure 1. Some drugs featuring alicyclic annulated triazoles

A main method for constructing such heterocyclic systems was proposed in the 1950s and is based on the reaction of cyclic imidates **V** with acid hydrazides (Figure 2).[19]

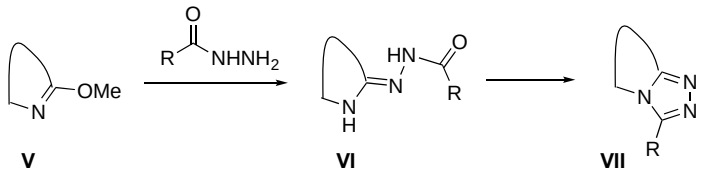


Figure 2. A main method for synthesis of annulated triazoles

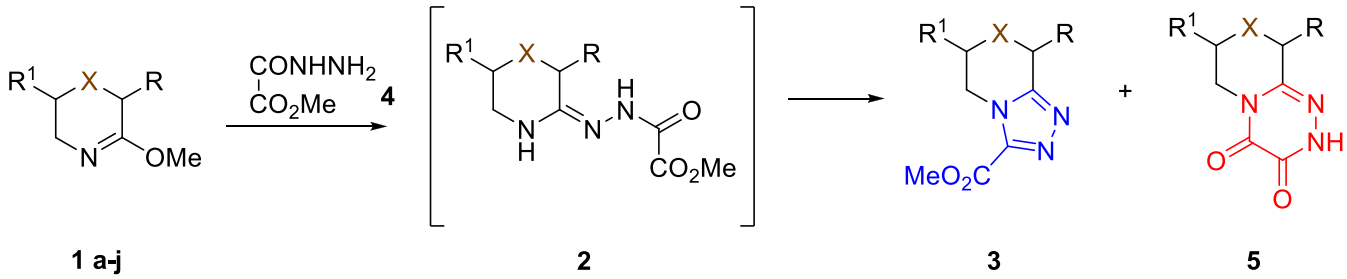
The reaction proceeds in two steps via the formation of cyclic amidrazone **VI** and its subsequent transformation into annulated triazole **VII**. Further studies have shown that the reaction conditions that should be applied greatly depend on the size of the saturated cycle of the starting cyclic imidate. Usually, for six-membered and larger cyclic imidates, boiling in alcohol the starting compounds leads to the target triazoles in one step. It is not possible to isolate intermediates **VI** under these conditions. In the case of five-membered cyclic imidates, under the same conditions only the intermediates **VI** are formed.[20–23] More stringent conditions are required to carry out the cyclization. Commonly, it can be accomplished by prolonged refluxing in acetic acid or by disilylation of amidrazones **VI** followed by cyclization in annulated triazoles **VII** under acidic conditions.[24] In some cases, the reaction is carried out by boiling the starting compounds in acetic acid. In most cases the need to apply stringent conditions for the cyclization of five-membered amidrazones **VI** led only to a decrease in the yield of the target triazoles. However, in the case of hydrazides bearing additional functional groups, an alternative reaction can take place.[25] In the literature there are only a few examples of the reactions of cyclic imidates with functionally substituted acid hydrazides. Nevertheless, this approach, on the one hand, makes it possible to obtain 3-functionalized

alicyclic annulated triazoles, and on the other hand, to find new ways of using the well-studied reaction for the synthesis of PSBH.

RESULTS AND DISCUSSION

Therefore, in this work we chose as an object of study the reaction of cyclic imidates with the simplest functionally substituted hydrazide - methyl 2-hydrazinyl-2-oxoacetate **4**. It was assumed that either esters of annulated triazole-3-carboxylic acids **3** or 1,2,4-triazine-5,6-dione derivatives **5** can be prepared.

In the literature there is almost no information on such compounds. For example, the synthesis of 5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine derivative **3**, R = R^1 = H, X = NH) was described by reducing the corresponding heteroaromatic bicycle.[26] Some 3,4-annulated 1,2,4-triazine-5,6-dione were obtained by a reaction of nitrogen heterocycles bearing hydrazine group with diethyloxalate.[27–29]



Scheme 1. The reaction of cyclic imidates **1** with hydrazide **4**

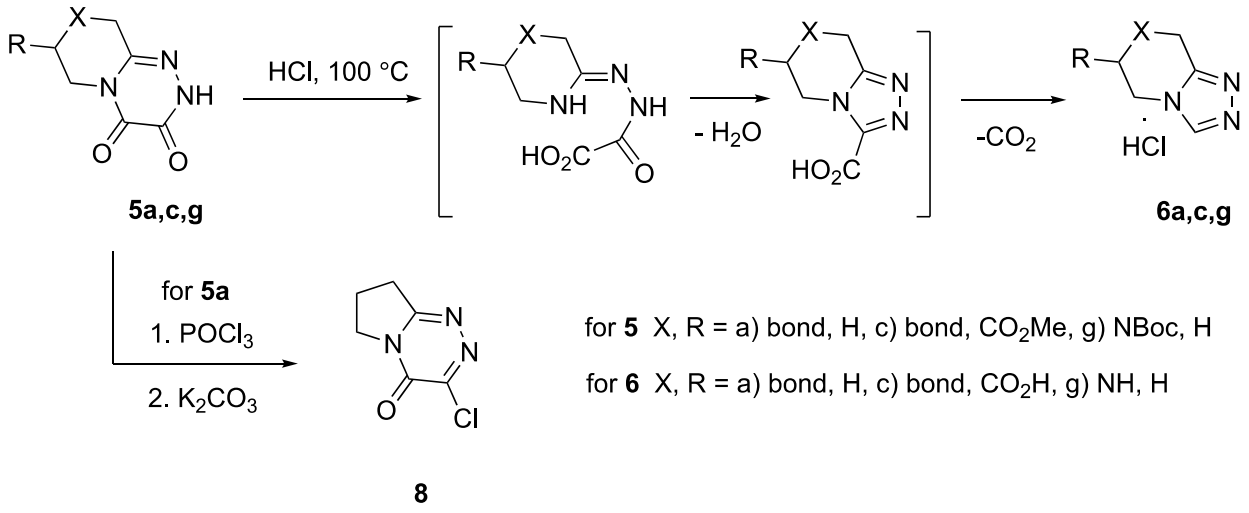
Table 1. Derivatives **3** and **5** synthesized via Scheme 1

Entry	Product				MeOH, 60 °C (Method A)		HOAc, 70 °C (Method B)	
	1, **3**, **5**	**X**	**R**	**R^1**	in the reaction mixture[a]		in the reaction mixture[a]	
					3, %	**5**, % ()[b]	**3**, % in () [b]	**5**, %
1	a	bond	H	H	-	100 (84.2)	traces	95.4
2	b	bond	OTBDMS	H	-	100 (76.8)	traces	88.9
3	c	bond	H	CO_2Me	-	100 (89.6)		
4	d	CH_2	H	H	89.7	traces	94.6 (86.7)	traces
5	e	CH_2	H	CF_3	80.7	19.3	87.8 (69.3)	12.2
6	f	O	H	H	25.3	74.7	98.9 (91.6)	traces
7	g	NBoc	H	H	3.4	96.3	67.3 (52.4)	9.2
8	h	$(CH_2)_2$	H	H	95.3	-	98.5 (92.7)	-
9	i	OCH_2	H	H	92.5	-	93 (83.1)	-
10	j	$(CH_2)_3$	H	H	89.7	-	99.3 (94.4)	-

[a]The content was determined by LCMS of the reaction mixture.

[b] Yield of an isolated product.

For our studies, we selected cyclic imidates with different ring sizes **1a,d-j**, featuring substituents **1b,c,e** as well as bearing heteroatoms in the ring **1f,g,i**. The reaction was carried out in accordance with the standard methods used for the synthesis of triazoles **3**. We applied two methods using the following conditions: boiling the reagents in methanol with a 10% excess of a cyclic imidate for 12 hours (Method A) and heating the reagents at the temperature 70 ^{o}C in acetic acid (Method B). Thereafter, the solvent was evaporated and the residue was analyzed by LCMS and (or) NMR spectroscopy. The major product was isolated, purified and identified. The results are shown in Table 1. First of all, it should be noted that in none of the cases we were able to isolate the intermediate amidrazone **VI**, even when the reaction was carried out at room temperature. Applying method A five-membered cyclic imidates **1a-c** (entries 1-3) gave 1,2,4-triazinedione derivatives **5a-c** almost quantitatively. In acetic acid (method B) the main products remained the same triazinediones **5a-c**, but traces of triazoles **3a-c** were also found (about 5% according to LCMS data). Seven- and eight-membered cyclic imidates **1h-j** gave exclusively triazoles **3h-j** regardless of the presence of a heteroatom in the cycle and the reaction conditions (entries 8 - 10) (Table 1, Scheme 1). In the case of six-membered cyclic imidates **1d-g**, the result depended on their structure and the reaction conditions. The valerolactam derivative **1d** reacted with **4** to give triazole **3d** in 90-95% yield depending on the reaction conditions. In both cases (methods A and B), triazinedione **5d** was detected in the reaction mixtures by NMR spectroscopy. The presence of a CF_3 substituent at C(5) in **1e** led to a sharp increase in the amount of compound **5** in the reaction mixture - 19.3% (method A) and 12.2% (method B). In these cases, we isolated only triazole **3e** in an analytically pure form. Replacing a CH_2 group with a heteroatom (entries 6, 7) completely changed the ratio of the products when the reaction had been carried out under by the method A. The amount of triazine-5,6-dione in the reaction mixture increased to 75% for **5f** (X = O), and for the case of **5g** (X = NBoc) it was formed almost quantitatively. Heating in acetic acid led to the opposite results - the main products were triazoles **3f,g** and in the case of the piperazine derivative, a noticeable amount of **5g** was observed, as well as decomposition products. Compounds **5f** and **5g** were easily isolated from the reaction mixture in multi-gram quantities due to their poor solubility in low polar solvents. As can be seen from Table 1, heating in acetic acid promotes the formation of the triazole ring. We tried to shift the reaction towards the formation of pyrrolo[2,1-*c*]-1,2,4-triazole derivatives by increasing the temperature and the reaction time. However, it turned out that boiling cyclic imidate **1a** and compound **4** in acetic acid for 48 hours almost quantitatively gave triazinedione **5a**. Like in the case of method B, the amount of triazole **3a**, determined by HPLC, in the mixture did not exceed 6 -7%.

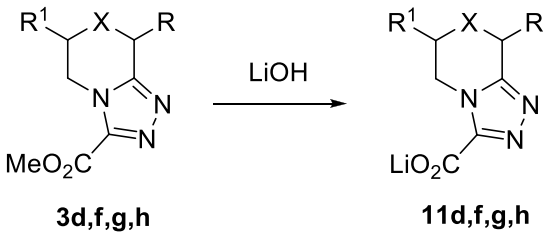


Scheme 2. Acid catalyzed transformation of triazinediones **5** into triazoles **6**

At the same time, boiling triazinediones **5a,c,g** in concentrated HCl resulted in almost quantitative formation of triazoles **6a,c,g** (Scheme 2). It can be assumed that in this case, under the action of aqueous hydrochloric acid, the triazine ring was opened and an intermediate product subsequently cyclized into the thermodynamically more stable triazole. The resulting triazole carboxylic acid was readily decarboxylated affording a triazole hydrochloride salt. A similar transformation was observed earlier for 6,7-dihydro-2*H*-thiazolo[2.3-*c*]-2,4,1-triazine-3,4-dione which, when treated with alkali at room temperature, gave 2,6-dihydrothiazolo[2,3-*c*]-1,2,4-triazole.[30] The key role of water in this process is indicated by the fact that when **5a** was treated with phosphorus oxychloride under analogous conditions, its recyclization to **6a** was not observed. Instead, chloro derivative **8** was formed as a result of the replacement of one of the oxygen atoms with chlorine. The chlorine atom in compound **8** is highly labile, which opens up additional possibilities for further modification of this heterocyclic system.

Summarizing our data, it can be concluded that the reaction of cyclic imidates with methyl 2-hydrazinyl-2-oxoacetate **4** mainly led to more thermodynamically stable triazoles **3**. Various structural and electronic factors can hamper the cyclization of amidrazones **2** into the triazoles **3**. Due to ring strain ensuing in the formation of the annulated 5+5 bicyclic compounds (entries 1-3), reduced basicity of the saturated cycle (entry 6) or steric hindrances (entries 5, 7) various amount of kinetically controlled compounds **5** was formed as well. In all cases acid catalysis promoted formation of triazole derivatives **3**.

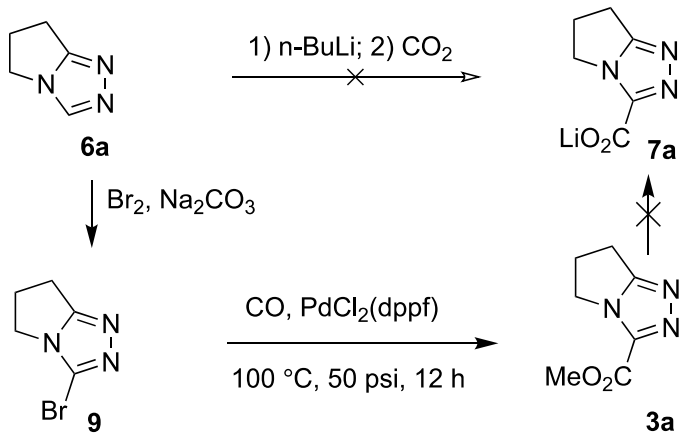
Esters **3d-h** readily hydrolyzed upon short heating with LiOH hydrate in methanol. The corresponding acids were isolated and identified in multi-gram amounts as lithium salts **11d-h** (Scheme 3).



3d,f,g,h **11d,f,g,h**

Scheme 3. Preparation of carboxylic lithium salts **7**

The corresponding free acids turned out to be unstable, and when the salts **7** were treated with inorganic acids, a mixture of products was observed as a result of their decarboxylation, even at room temperature. We attempted to prepare lithium salt of 5*H*-6,7-pyrrolo[2,1-*c*]-1,2,4-triazole-3-carboxylic acid **7a** by lithiation of the triazole ring **6a** followed by treatment with CO_2 (Scheme 4).



Scheme 4. Attempted synthesis of free carboxylic acids

As a result, we obtained an inseparable mixture of the starting product **6a** and salt **7a**. Therefore, a different approach was used to obtain derivatives of 5*H*-6,7-pyrrolo[2,1-*c*]-1,2,4-triazole-3-carboxylic acid. Bromination of **6a** with elemental bromine in the presence of sodium carbonate gave bromo derivative **9** in a high yield. Subsequent carbonylation of **9** catalyzed by $PdCl_2$(dppf) gave ester **3a** in a moderate yield. However, all attempts to hydrolyze **3a** to the corresponding carboxylic acid were unsuccessful, since partial decarboxylation proceeded leading to a mixture of compounds **6a** and **7a**.

Summing up, the reaction of cyclic imidates with methyl 2-hydrazinyl-2-oxoacetate serves as a convenient method for the synthesis of multi-gram amounts of alicyclic annulated triazole carboxylic acids. In the case of five- and six-membered cyclic imidates the reaction can be used for synthesis of 1,2,4-triazine-5,6-diones derivatives. Under acidic conditions the latter can be transformed into triazoles.

EXPERIMENTAL

Solvents were purified and dried by standard methods. Melting points were determined with an electrothermal capillary melting point apparatus. ^{1}H NMR spectra were recorded with Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR), Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR). Chemical shifts are reported in ppm relative to internal tetramethylsilane (TMS; for ^{1}H and ^{13}C). Elemental analyses were performed at the analytical laboratory of Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

Method A:

To a stirred solution of cyclic imidate **1** (279 mmol, 1.1 eq.) in anhydrous MeOH (100 mL) was added methyl 2-hydrazinyl-2-oxoacetate **4** (30 g, 254 mmol.) and the suspension was heated at 60 ºC for 12 h.

Method B:

To a stirred solution of cyclic imidate **1** (327 mmol, 1.1 eq.) in acetic acid (100 mL) was added methyl 2-hydrazinyl-2-oxoacetate **4** (35 g, 297 mmol) and the reaction mixture was heated at 70 ºC for 12 h. The resulting solution was cooled to room temperature and filtered. Volatiles were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (350 mL), washed with saturated aqueous solution of K_2CO_3 (3×70 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by recrystallization from toluene to afford the corresponding triazolo-3-carboxylate **3**.

Methyl 6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-3-carboxylate **(3a).** To a solution of **9** (0.5 g, 2.66 mmol) in MeOH (15 mL) was added Pd(dppf)Cl_2×CH_2Cl_2 (0.22 g, 0.27 mmol, 10 mol%) followed by triethylamine (0.8 g, 7.98 mmol, 3 eq.). The resulting mixture was carbonylated under CO atmosphere at 100 ºC and 50 Psi and left for 12 h. The reaction mixture was cooled, volatiles were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (10×3 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The obtained purple powder was dissolved in Et_2O (10 mL). Impurities were removed by filtration, Et_2O was evaporated under reduced pressure to give pale yellow solid, yield 48.1% mp 115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, *J* = 7.2 Hz, 3H), 3.97 (s, 4H), 3.01 (t, *J* = 7.7 Hz, 3H), 2.80 (p, *J* = 7.4 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 164.99, 158.16, 142.93, 52.88, 45.48, 28.44, 21.40. LCMS (ES-API) *m/z* = 168.0 $(M+H)^+$, 169.0 $(M+H)^+$ Anal. Calcd for $C_7H_9N_3O_2$ (167.17): C 50.30, H 5.43, N 25.14. Found: C 50.42, H 5.45, N 25.08.

Methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate **(3d).** Method A. The resulting solution was evaporated under reduced pressure to afford a crude product as a beige solid. It was dissolved in CH_2Cl_2, washed with saturated aqueous solution of K_2CO_3, dried over anhydrous Na_2SO_4. Volatiles were

evaporated, the residue was recrystallized from PhMe to give the target triazolo-3-carboxylate **3d** as a white powder. Yield 70.6%, mp 148-150 ºC. The compound was prepared by method B as well. Yield 86.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, *J* = 6.1 Hz, 2H), 3.94 (s, 3H), 3.00 (t, *J* = 6.4 Hz, 2H), 2.04 – 1.94 (m, 2H), 1.95 – 1.85 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.6, 154.4, 144.5, 52.8, 45.3, 22.2, 19.2. LCMS (ES-API) *m/z* = 182.2 $(M+H)^+$. Anal. Calcd for $C_8H_{11}N_3O_2$ (181.20): C 53.03, H 6.12, N 23.19. Found: C 53.14, H 6.08, N 23.11.

Methyl 6-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate **(3e).** Method A. The resulting solution was evaporated under reduced pressure to afford a crude product as a beige solid. It was dissolved in CH_2Cl_2, washed with saturated aqueous solution of K_2CO_3, dried over anhydrous Na_2SO_4. Volatiles were evaporated; the residue was recrystallized from PhMe to give the target triazolo-3-carboxylate **3e** as a white powder. Yield 49.3%, mp 174-175 ºC. The compound was prepared by method B. Yield 69.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 14.1, 5.7 Hz, 1H), 4.15 (dd, *J* = 14.0, 10.4 Hz, 1H), 3.98 (s, 3H), 3.34-3.27 (m, 1H), 3.01-2.92 (m, 1H), 2.84 – 2.78 (m, 1H), 2.37-2.3 (m, 1H), 2.0-1.9 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 153.0, 144.2, 125.9 (q, *J* = 279.0 Hz), 52.9, 43.4, 38.3 (q, *J* = 28.4 Hz), 20.5, 19.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.1. LCMS (ES-API) *m/z* = 250.0 $(M+H)^+$.
Anal. Calcd for $C_9H_{10}F_3N_3O_2$ (249.19): C 43.38, H 4.04, N 16.86. Found: C 43.48, H 4.09, N 16.79.

Methyl 6,8-dihydro-5H-[1,2,4]triazolo[3,4-c][1,4]oxazine-3-carboxylate **(3f).** Method B. White crystalline powder. Yield 91.6%, mp 153-155 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.96 (s, 2H), 4.28 (t, *J* = 5.3 Hz, 2H), 4.00 (t, *J* = 5.3 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.2, 151.3, 144.7, 63.1, 62.7, 52.9, 45.0. LCMS (ES-API) *m/z* = 184.2 $(M+H)^+$. Anal. Calcd for $C_7H_9N_3O_3$ (183.17): C 45.90, H 4.95, N 22.94. Found: C 45.83, H 4.91, N 23.02.

7-tert-Butyl 3-methyl 5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-3,7(8H)-dicarboxylate **(3g).** Method B. Beige poder, mp 107-110 ºC, Yield 52.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.75 (s, 2H), 4.27 (t, *J* = 5.5 Hz, 2H), 3.90 (s, 3H), 3.76 (t, *J* = 5.5 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0, 153.7, 150.8, 144.2, 81.6, 52.8, 44.7, 28.2, 28.1. LCMS (ES-API) *m/z* = 282.2 $(M+H)^+$, 284.2 $(M+H)^+$.
Anal. Calcd for $C_{12}H_{18}N_4O_4$ (282.30): C 51.06, H 6.43, N 19.85. Found: C 50.95, H 6.37, N 19.92.

Methyl 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine-3-carboxylate **(3h).** Method A. The resulting solution was evaporated under reduced pressure to afford a crude product as a beige solid. It was dissolved in CH_2Cl_2, washed with saturated aqueous solution of K_2CO_3, dried over anhydrous Na_2SO_4, and concentrated. The residue was recrystallized from PhMe to give the target triazolo-3-carboxylate as a white powder. Yield 84.2%, mp 112 -114 ºC. Compound **3h** was prepared by method B in 92.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.48 (br. s, 2H), 3.88 (s, 3H), 2.98 (br. s, 2H), 1.81 (br. s, 2H), 1.70 (br. s, 2H), 1.60 (br. s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.5, 159.0, 145.0, 52.9, 45.7, 30.1, 27.9, 26.1, 25.1.

LCMS (ES-API) *m/z* = 196.2 $(M+H)^+$, 197.2 $(M+H)^+$. Anal. Calcd for $C_9H_{13}N_3O_2$ (195.22): C 55.37, H 6.71, N 21.52. Found: C 55.45, H 6.77, N 21.48.

***Methyl 5,6,8,9-tetrahydro-[1,2,4]triazolo[4,3-d][1,4]oxazepine-3-carboxylate* (3i).** Method A. The resulting solution was evaporated under reduced pressure to afford a crude product as a beige solid. It was dissolved in CH_2Cl_2, washed with saturated aqueous solution of K_2CO_3, dried over anhydrous Na_2SO_4, and concentrated. The residue was recrystallized from PhMe to give the target triazolo-3-carboxylate **3i** as a white powder. Yield 81.4%, mp 153 -155 °C. Compound **3i** was prepared by method B in 83.1% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 – 4.74 (m, 2H), 3.98 (s, 3H), 3.92 – 3.84 (m, 4H), 3.34 – 3.26 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.6, 144.8, 69.8, 67.8, 52.9, 48.6, 30.2. LCMS (ES-API) *m/z* = 198.2 $(M+H)^+$, 199.2 $(M+H)^+$. Anal. Calcd for $C_8H_{11}N_3O_3$ (197.20): C 48.73, H 5.62, N 21.31. Found: C 48.64, H 5.65, N 21.38.

***Methyl 5,6,7,8,9,10-hexahydro-[1,2,4]triazolo[4,3-a]azocine-3-carboxylate* (3j).** Method A. The resulting solution was evaporated under reduced pressure to afford a crude product as a beige solid. It was dissolved in CH_2Cl_2, washed with saturated aqueous solution of K_2CO_3, dried over anhydrous Na_2SO_4, and concentrated. The residue was recrystallized from PhMe to give the target triazolo-3-carboxylate **3j** as a white powder. Yield 78.5%, mp 150 -153 °C. Compound **3j** was prepared by method B in 94.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (t, *J* = 6.1 Hz, 2H), 3.91 (s, 3H), 2.91-2.88(m, 2H), 1.82 – 1.73 (m, 4H), 1.49-1.45 (m, 2H), 1.19-1.14 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 158.4, 144.3, 52.6, 43.0, 30.4, 30.0, 25.3, 24.4, 23.2. LCMS (ES-API) *m/z* = 210 $(M+H)^+$. Anal. Calcd For $C_{10}H_{15}N_3O_2$ (209.25): C 57.40, H 7.23, N 20.08. Found: C 57.51, H 7.18, N 20.15.

***7,8-Dihydropyrrolo[2,1-c][1,2,4]triazine-3,4(2H,6H)-dione* (5a).** Method A. The resulting solution was reduced in volume to 2/3, filtered off and washed 3 times with Et_2O to give pure triazinedione **5a** as a white powder. Yield 84.2%, mp 177-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 3.85 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.8 Hz, 2H), 2.14-2.07 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.9, 154.9, 148.5, 46.6, 28.9, 20.8. LCMS (ES-API) *m/z* = 154.2 $(M+H)^+$, 155.0 $(M+H)^+$. Anal. Calcd for $C_6H_7N_3O_2$ (153.14): C 47.06, H 4.61, N 27.44. Found: C 46.97, H 4.56, N 27.51.

***8-((tert-Butyldimethylsilyl)oxy)-7,8-dihydropyrrolo[2,1-c][1,2,4]triazine-3,4(2H,6H)-dione* (5b).** Method A. The resulting solution was evaporated under reduced pressure, triturated with Et_2O, filtered off and washed 3 times with Et_2O to give pure triazinedione **5b** as a white powder. Yield 76.8%, mp 165-170 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 5.03 (t, *J* = 6.5 Hz, 1H), 3.93-3.90 (m, 1H), 3.76-3.70 (m, 1H), 2.46-2.38 (m, 1H), 2.01-1.93 (m, 1H), 0.88 (s, 9H), 0.12 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.0, 154.6, 148.3, 71.2, 43.2, 31.9, 26.0, 18.3, -4.3, -4.5. LCMS (ES-API) *m/z* = 284.2 $(M+H)^+$. Anal. Calcd for $C_{12}H_{21}N_3O_3Si$ (283.41): C 50.86, H 7.47, N 14.83. Found: C 50.97, H 7.41, N 14.89.

Methyl 3,4-dioxo-2,3,4,6,7,8-hexahydropyrrolo[2,1-c][1,2,4]triazine-7-carboxylate **(5c).** Method A. The precipitate was collected by filtration, washed 3 times with MeOH and Et_2O to give pure triazinedione **5c** as a white solid. Yield 89.6%, mp 175 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.17 (s, 1H), 4.12-4.00 (m, 2H), 3.67 (s, 3H), 3.63 – 3.54 (m, 1H), 3.17 – 3.04 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.5, 154.8, 154.5, 146.7, 52.8, 48.2, 38.4, 31.8. LCMS (ES-API) *m/z* = 212.0 $(M+H)^+$, 213.0 $(M+H)^+$. Anal. Calcd for $C_8H_9N_3O_4$ (211.18): C 45.50, H 4.30, N 19.90. Found: C 45.42, H 4.26, N 19.96.

6,7-Dihydro-[1,4]oxazino[3,4-c][1,2,4]triazine-3,4(2H,9H)-dione **(5f).** Method A. The precipitate was collected by filtration, washed 3 times with MeOH and Et_2O to give pure triazinedione **5f** as a white solid. Yield 91.6%, mp 225-227 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.29 (s, 1H), 4.44 (s, 2H), 4.01 – 3.89 (m, 2H), 3.70 (t, *J* = 6.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.2, 154.5, 139.0, 64.8, 63.6, 41.0. LCMS (ES-API) *m/z* = 169.9 $(M+H)^+$. Anal. Calcd for $C_6H_7N_3O_3$ (169.14) C 42.61, H 4.17, N 24.84. Found: C 42.70, H 4.21, N 24.77.

tert-Butyl 3,4-dioxo-3,4,6,7-tetrahydro-2H-pyrazino[2,1-c][1,2,4]triazine-8(9H)-carboxylate **(5g).** Method A. The resulting solution was evaporated to give a light yellow oil. It was triturated with EtOH to give a beige powder. Yield 52.4%, mp 157-159 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 4.30 (s, 2H), 3.94 (s, 2H), 3.56 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.1, 154.1, 153.4, 139.4, 79.9, 52.5, 27.9. LCMS (ES-API) *m/z* = 269.0 $(M+H)^+$. Anal. Calcd for $C_{11}H_{16}N_4O_4$ (268.27): C 49.25, H 6.01, N 20.88. Found: C 49.33, H 6.06, N 20.81.

6,7-Dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole hydrochloride **(6a).** Compound **3a** (2 g, 13.1 mmol) was dissolved in concentrated HCl (50 mL). The reaction mixture was refluxed for 24 h. It was cooled to room temperature and volatiles were evaporated under reduced pressure. The residue was the target salt **6** as a white powder 1.89 g. Yield 99%, mp 187 -190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (br. s, 1H), 9.65 (s, 1H), 4.27 (t, *J* = 7.3 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.72 (p, *J* = 7.5 Hz, 2H).^{13}C NMR (126 MHz, DMSO-d_6) δ 161.6, 139.6, 45.9, 27.3, 20.9. LCMS (ES-API) *m/z* = 110.2 $(M+H)^+$. Anal. Calcd for $C_5H_8ClN_3$ (145.59): C 41.25, H 5.54, N 28.86. Found: C 41.18, H 5.58, N 28.78.

6,7-Dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole-6-carboxylic acid hydrochloride **(6c).** White solid, yield 95.2%, mp = 193-195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 2H), 9.63 (s, 1H), 4.54 (dd, *J* = 11.8, 9.1 Hz, 1H), 4.43 (dd, *J* = 11.7, 6.4 Hz, 1H), 4.19-4.12 (m, 1H), 3.42 (dd, *J* = 17.2, 9.6 Hz, 1H), 3.30 (dd, *J* = 17.1, 6.6 Hz, 1H).^{13}C NMR (126 MHz, DMSO-d_6) δ 172.2, 160.1, 139.7, 47.8, 45.5, 24.5.
LCMS (ES-API) *m/z* = 154.2 $(M+H)^+$, 155.1 $(M+H)^+$. Anal. Calcd for $C_6H_8ClN_3O_2$ (189.60): C 38.01, H 4.25, N 22.16. Found: C 37.93, H 4.21, N 22.24.

5,6,7,8-Tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine dihydrochloride **(6g).** Beige powder, yield 93.1%, mp 132-133 °C. ^{1}H NMR (400 MHz, D_2O) δ 4.04 (s, 2H), 3.51-3.48 (m, 2H), 3.43-3.40 (m, 2H).^{13}C NMR (151

MHz, D_2O) δ 168.51, 162.58, 47.72, 43.96, 35.36. LCMS (ES-API) *m/z* = 125.2 $(M+H)^+$, 126.0 $(M+H)^+$. Anal. Calcd for $C_5H_{10}Cl_2N_4$ (197.07): C 30.47, H 5.11, N 28.43. Found: C 30.56, H 5.06, N 28.35.

General procedure for the preparation of lithium salts 7d,f,g,h.

To a stirred solution of methyl ester **3** (0.95 eq.) in MeOH (150 mL) was added lithium hydroxide (1 eq.). The reaction mixture was heated at 60 ºC for 12 h. It was allowed to cool to room temperature. The reaction mixture was filtered off. The solvent was evaporated till dryness under reduced pressure. The residue was dissolved in boiling acetone (50 mL). The hot solution was filtered to remove admixtures. The solution was cooled to room temperature to give a white solid that was collected by filtration.

Lithium 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate **(7d).** White solid, yield 91.1%, mp 156 ºC. ^{1}H NMR (500 MHz, D_2O) δ 4.12 (t, *J* = 5.1 Hz, 2H), 2.79 (t, *J* = 5.2 Hz, 2H), 1.89 – 1.80 (m, 2H), 1.80 – 1.72 (m, 4H).^{13}C NMR (126 MHz, D_2O) δ 163.0, 154.1, 149.8, 44.9, 21.6, 21.3, 18.4. LCMS (ES-API) *m/z* = 168.2 $(M+H)^+$. Anal. Calcd for $C_7H_8LiN_3O_2$ (173.10): C 48.57, H 4.66, N 24.28. Found: C 48.48, H 4.70, N 24.22.

Lithium 6,8-dihydro-5H-[1,2,4]triazolo[3,4-c][1,4]oxazine-3-carboxylate **(7f).** White solid, yield 84.1%, mp 238-240 ºC. ^{1}H NMR (500 MHz, D_2O) δ 4.92 (t, *J* = 4.9 Hz, 2H), 4.29 (t, *J* = 4.7 Hz, 2H), 4.04 (t, *J* = 4.5 Hz, 2H).^{13}C NMR (126 MHz, D_2O) δ 162.2, 150.0, 149.6, 63.2, 62.2, 44.4. LCMS (ES-API) *m/z* = 170 $(M+H)^+$. Anal. Calcd for $C_6H_6LiN_3O_3$ (175.07): C 41.16, H 3.45, N 24.00. Found: C 41.24, H 3.48, N 23.92.

Lithium 7-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylate **(7g).** White solid, yield 69.7%, mp 172 ºC. ^{1}H NMR (500 MHz, D_2O) δ 4.80 (s, 2H), 4.34 (t, *J* = 5.3 Hz, 2H), 3.84 (s, 2H), 1.43 (s, 9H).^{13}C NMR (126 MHz, D_2O) δ 162.3, 155.7, 149.9, 149.8, 82.7, 44.4, 27.5. LCMS (ES-API) *m/z* = 225.2 $(M+H)^+$, 227.2 $(M+H)^+$. Anal. Calcd for $C_{11}H_{15}LiN_4O_4$ (274.21): C 48.18, H 5.51, N 20.43. Found: C 48.27, H 5.57, N 20.36.

Lithium 6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine-3-carboxylate **(7h).** White solid, yield 89.5%, mp = 160-162 ºC. ^{1}H NMR (500 MHz, D_2O) δ 4.43-4.41 (m, 2H), 2.97-2.95 (m, 2H), 1.88-1.84 (m 2H), 1.77-1.73 (m, 2H), 1.69-1.65 (m, 2H).^{13}C NMR (126 MHz, D_2O) δ 163.1, 159.4, 150.9, 45.5, 29.3, 27.1, 25.2, 24.1. LCMS (ES-API) *m/z* = 138.2 $(M+H)^+$, 139.2 $(M+H)^+$. Anal. Calcd for $C_8H_{10}LiN_3O_2$ (187.13): C 51.35, H 5.39, N 22.46. Found: C 51.43, H 5.43, N 22.39.

3-Chloro-7,8-dihydropyrrolo[2,1-c][1,2,4]triazin-4(6H)-one **(8).** To 2,6,7,8-tetrahydropyrrolo[2,1-*c*][1,2,4]triazine-3,4-dione (10 g, 65.4 mmol) was added phosphorus oxychloride (100 mL), the mixture was heated at 100 ºC for 2 h. Then phosphorus oxychloride was evaporated under reduced pressure, residue was frozen by liquid nitrogen and added to potassium carbonate with ice. The mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to provide the title compound (6 g). Brown powder, yield = 53.5%, mp 125-136 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (t, *J* = 8 Hz, 2H), 3.22 (t, *J* = 8.0 Hz, 2H), 2.32 (p, *J* = 7.8 Hz,

2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 161.01, 152.08, 149.11, 48.13, 30.69, 19.77. LCMS (ES-API) *m/z* = 172.0 $(M+H)^+$, 174.0 $(M+H)^+$, 175.0 $(M+H)^+$. Anal. Calcd for $C_6H_6ClN_3O$ (171.59): C 42.00, H 3.52, Cl 20.66, N 24.49. Found: C 42.11, H 3.48, Cl 20.74, N 24.57.

***3-Bromo-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole* (9).** 6,7-Dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazole hydrochloride (5 g, 34.3 mmol) was suspended in CH_2Cl_2 (40 mL), few drops of water and K_2CO_3 (until basic pH) was added. Solid residue was removed by filtration, the filtrate was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give free base of the title compound as a white solid. 6,7-Dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazole (3.65 g, 33.4 mmol) was dissolved in CH_2Cl_2 (100 mL) and Na_2CO_3 (5.32 g, 1.5 eq.) was added. The mixture was cooled to 0 °C and bromine (5.61 g, 1.05 eq.) was added. The reaction mixture was stirred overnight at room temperature; water (50 mL) was added. The organic layer was separated and washed with water (3×50 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give compound **9**. Orange solid, 84.3% yield, mp 107 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.94 (t, *J* = 7.2 Hz, 1H), 2.91 (t, *J* = 7.6 Hz, 1H), 2.66 (p, *J* = 7.3 Hz, 1H).^{13}C NMR (151 MHz, DMSO-d_6) δ 164.45, 122.72, 43.40, 29.51, 27.42, 21.31. MS-EI: *m/z* 187 (100%), 133 (10%), 80 (35%), 53 (50%), 39 (12%). Anal. Calcd for $C_5H_6BrN_3$ (188.03): C 31.94, H 3.22, N 22.35. Found: C 31.86, H 3.17, N 22.27.

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