HETEROCYCLES, Vol. 91, No. 2, 2015, pp. 363 - 374. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 16th October, 2014, Accepted, 26th December, 2014, Published online, 7th January, 2015
DOI: 10.3987/COM-14-13109

MODIFICATION OF 3,5-DIOXO-2-PHENYL-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINE-6-CARBONITRILE VIA MITSUNOBU AND CHAN-LAM COUPLING REACTION

Tomáš Ručil, Martin Grepl, and Petr Cankař*

Department of Organic Chemistry, Palacky University, 17. listopadu 1192/12, 771 46 Olomouc, Czech Republic
E-mail: cankar@orgchem.upol.cz

Abstract − Modification of 3,5-dioxo-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile at position 4 is described. Alkylations were carried out under Mitsunobu reaction conditions in DCM or dioxane with alcohols containing tertiary amines, pyridine and imidazole heterocyclic systems, and Boc-protected amino groups. The scope of modifications was extended with arylations performed via Chan-Lam coupling reaction using copper(I) oxide as a catalyst in a DMF solution at room temperature. In order to further extend peripheral structural diversity the nitrile group at position 6 of several alkylated 1,2,4-triazines was transformed into the amidoxime functionality.

The compounds containing the 1,2,4-triazine-3,5(2*H*,4*H*)-dione moiety (**II**) belong to a group of heterocycles that are very similar to pyrimidine bases, especially to uracil (**III**) (Figure 1). For this reason 1,2,4-triazines (**I**) have appeared as a subject of many biological studies.[1] Recently, several reports have indicated that substitution of the 1,2,4-triazine moiety in position 2, 4, and 6 is favourable for biological activity as c-Met kinase inhibitors,[2] cathepsin K inhibitors,[3] GABA subtype B receptor modulators,[4] $P2X_7$ receptor antagonists[5] or antagonists of the gonadotropin-releasing hormone receptor.[6]

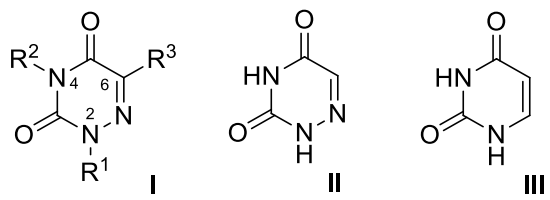
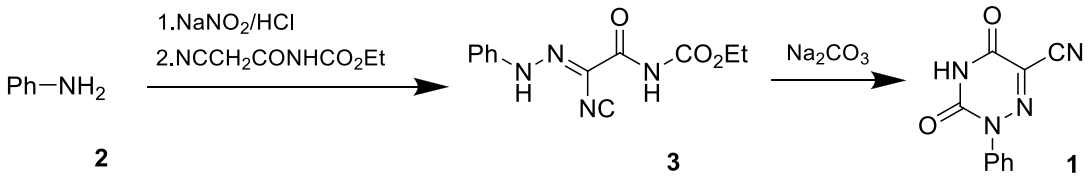


Figure 1. Structural similarity of triazine (**I**)

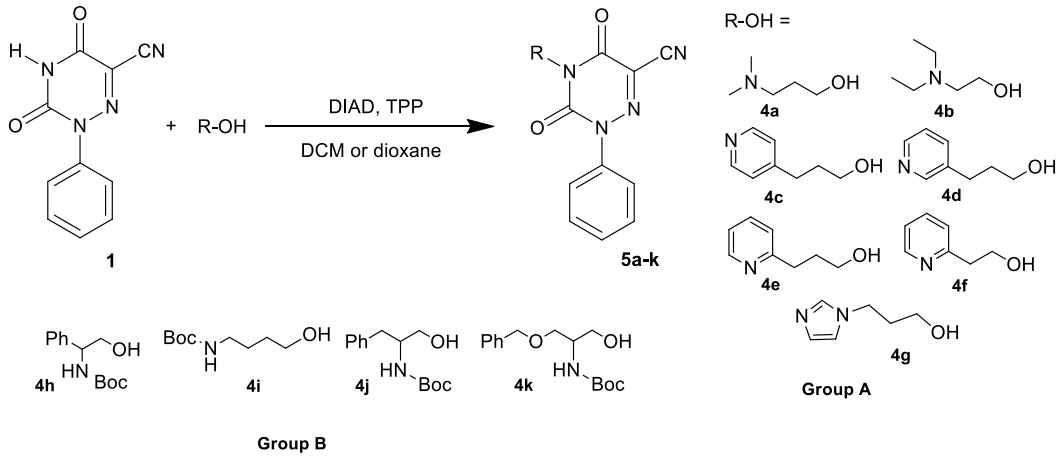
In this paper we focused on a preliminary study to modify position 4 in 1,2,4-triazine (**I**) system via Mitsunobu and Chan-Lam coupling reaction since these methodologies enable to synthesize derivatives with the extended scope of alkyl or aryl structural diversity. For this purpose phenyltriazinedione (**1**) was prepared as a model starting compound via reported synthesis by Slouka (Scheme 1).[7]



Scheme 1. Synthesis of starting 1,2,4-triazine (**1**)

Substitutions at position 4 in 1,2,4-triazine (**1**) were usually carried out via classical *N*-alkylation methods using alkyl iodides[3] or alkyl bromides.[3,5] Alternatively, modifications were accomplished with substituted oxirans[5] and, more recently, one example of Pd-catalyzed hydroamidation reaction with isoprene was described.[8] However, especially classical alkylation methods have limitations in regioselectivity or availability of reagents. Moreover, higher temperature of a reaction mixture has to be maintained. In comparison to classical alkylation methods the Mitsunobu reaction offers milder reaction conditions and extended structural diversity of an alkyl moiety.

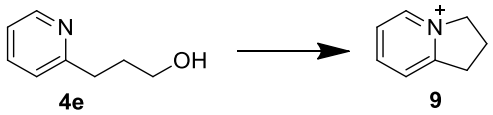
To use triazine (**1**) as a Mitsunobu nitrogen nucleophile is enabled by the relatively strong acidic N-H bound. Several years ago, Chen reported one example of Mitsunobu reaction on a similar 1,2,4-triazine system,[6] however, this reaction was not studied more in detail. In connection with this report we decided to study alkylation of 1,2,4-triazine (**1**) at position 4 with a set of alcohols (**4a-k**) to bring a more detailed insight into Mitsunobu reaction (Scheme 2).



Scheme 2. Alkylation of triazine (**1**) via Mitsunobu reaction

The study was commenced with aliphatic aminoalcohols (**4a**) and (**4b**) in DCM and dioxane solutions. In both cases, dioxane proved to be a more convenient solvent (Entry **5a** and **5b**). In the case of use of alcohol (**4b**), the yield of the corresponding triazine (**5b**) was reduced due to formation of side products, which also decreased its purity.

Aminoalcohols containing heteroaryl moiety (**4c-g**) have to be treated with an additional amount of reagents in a DCM solution after 1 hour. However, if dioxane was used instead of DCM (Entry **5c-g**), the yields were always significantly higher. Aminoalcohol (**4e**) did not react with triazine (**1)** (Entry **5e**) most likely due to a preferred formation of pyridinium salt (**9**),[9] which was detected by the LC-MS analysis (Scheme 3).



4e **9**

Scheme 3. Assumed formation of pyridinium salt (**9**)

Table 1. Mitsunobu reaction

Entry	R-OH	Methods[a]	React. time	Yield/Purity[b] (%)
5a	*N*,*N*-dimethylaminopropan-l-ol (**4a**)	A,C	2h	46/96 , 60/90
5b	*N*,*N*-diethylaminoethanol (**4b**)	A,C	2.5h	33/85[c] , 40/88[c]
5c	3-pyridin-4-ylpropan-1-ol (**4c**)	B,C	24h , 2h	75/99 , 85/95
5d	3-pyridin-3-ylpropan-1-ol (**4d**)	B,C	24h , 2h	55/95 , 92/95
5e	3-pyridin-2-ylpropan-1-ol (**4e**)	A, B, C	24h-10days	-/-
5f	2-pyridin-2-ylethanol (**4f**)	B,C,D	24h	50/90 , 80/92, 81/99
5g	2-imidazol-1-ylpropanol (**4g**)	B,C	24h	46/95 , 67/99
5h	(2-hydroxy-1-phenylethyl)*tert*-butylcarbamate (**4h**)	B,C	2h	0/0 , 60/93
5i	(3-hydroxybutyl)*tert*-butylcarbamate (**4i**)	C	2h	70/99.8
5j	(1-hydroxymethyl-2-phenylethyl)*tert*-butylcarbamate (**4j**)	C	1.5h	78/98
5k	(1-(benzyloxy)-3-hydroxypropan-2-yl)*tert*-butylcarbamate (**4k**)	C	1.5h	70/95

[a]Methods: **A=** 1 equiv. triazine, 1 equiv. alcohol, 1.5 equiv. TPP and 1.5 equiv. DIAD, rt, DCM; **B=** 1 equiv. triazine, 1 equiv. alcohol, 1.5 equiv. TPP and 1.5 equiv. DIAD, after 1h, reagents were added again (1.5 equiv. TPP and 1.5 equiv.DIAD), rt, DCM; **C=** 1 equiv. triazine 1 equiv. alcohol, 1.5 equiv. TPP and 1.5 equiv. DIAD, rt, 1,4-dioxane; **D=** 0.25 mmol of triazine, 0.275 mmol of alcohol, TPP (0.32g, 100-200 mesh, loading ~1.6 mmol/g) and 0.4 mmol of DIAD, rt, 1,4-dioxane.

[b]Purity was estimated on the basis of LC-MS analyses.

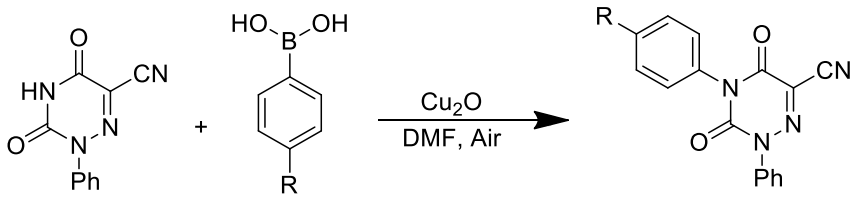
[c]Product was only detected via the LC-MS analysis. Further characterization was not performed due to a low purity of the product even after chromatography.

This hypothesis can be indirectly supported by reactivity of aminoalcohol (**4f**) where a shorter aliphatic chain did not allowed a similar cyclization so the reaction proceeded to the desired alkylated triazine (**5f**) (Entry **5f**). The isolation of triazine (**5f**) was complicated since triphenylphosphine was not possible to remove sufficiently even by chromatography. This drawback was eliminated with polymer-supported triphenylphosphine (Method D, Entry **5f**).

Aminoalcohol (**4h**) was chosen as a model compound of a set of Boc-protected aminoalcohols (**4h-k**) to examine the methodologies using DCM or dioxane. It was found that even after an addition of reagents in a DCM solution (Method B) the reaction did not take place (Entry **5h**). For this reason only the Method C using dioxane was applied for Boc-protected aminoalcohols (**4h-k**) (Entry **5h-k**) to synthesize triazines (**5h-k**).

Subsequently, deprotection of Boc group was studied at triazines (**5h-k**). Commonly used acid reagents such as hydrochloric acid, trifluoroacetic acid or sulfuric acid caused dealkylation or, moreover, a degradation of a 1,2,4-triazine ring. Application of an oxidative reagent, ammonium cerium(IV) nitrate, provided better results, however, the purity was not still sufficient.

In order to extend the scope of modifications with aryl moieties the Chan-Lam coupling reaction[10] was chosen as a complimentary method to Mitsunobu reaction. Several years ago, a standard procedure using copper(II) acetate was applied at the position 2 in a similar 1,2,4-triazine derivative only with 3-(trifluoromethyl)phenylboronic acid.[3] Initially, we decided to use this procedure to treat 1,2,4-triazine (**1**) with *p*-tolylboronic acid (**6a**) at position 4 (Scheme 4). Despite the desired product was formed the result was not still satisfactory. Consequently copper(II) acetate was changed for copper(I) oxide which was also described as an efficient catalyst for Chan-Lam coupling reaction under base-free reaction conditions.[11] This catalyst proved to be superior for arylation at position 4 (Entry **7a**).



1 **6a: R = Me** **6b: R = OMe** **6c: R = H** **6d: R = CF_3** **6e: R = NO_2** **7a-e**

Scheme 4. Chan-Lam coupling

Arylations with 4-methoxyphenyl and phenylboronic acid (Entry **7b-c**) gave triazines (**7b-c**) at moderate yield as well. If benzene ring was deactivated by trifluoromethyl or nitro group, the reaction practically

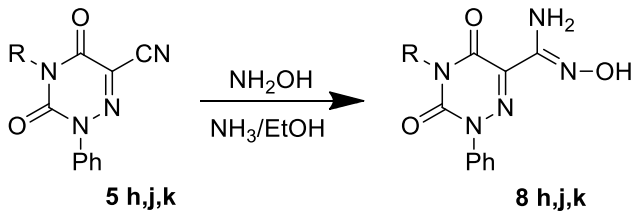
did not take place (Entry **7d-e**) even after 96 hours, only traces of desired products were observed.

Table 2. Chan-Lam coupling reaction

Entry	Boronic acid	React. time	Yield/purity[a] (%)
7a	*p*-tolylboronic acid (**6a**)	48h	55/99
7b	(4-methoxyphenyl)boronic acid (**6b**)	48h	56/99
7c	phenylboronic acid (**6c**)	48h	56/99
7d	(4-(trifluoromethyl)phenyl)boronic acid (**6d**)	96h	-/-[b]
7e	(4-nitrophenyl)boronic acid (**6e**)	96h	-/-[b]

[a]Purity was estimated on the basis of the LC-MS analysis.
[b]Only traces were observed via the LC-MS analysis.

Previously, the nitrile groups were transformed to other functionalities in similar triazines.[12] These studies let us to examine the reactivity of the nitrile group in substituted triazines (**5h, j,** and **k**) with hydroxylamine, alanine ethyl ester, and ethyl carbazate. However, the reaction underwent only with hydroxylamine resulting in triazines (**8h, j,** and **k**) (Scheme 5).



5 h,j,k **8 h,j,k**

Scheme 5. Addition of hydroxylamine to the nitrile group

In conclusion, herein reported results demonstrated that methods based on Mitsunobu and Chan-Lam coupling reaction can be useful for substitution of 1,2,4-triazine-3,5(2*H*,4*H*)-dione moiety at position 4. Also the nitrile group at position 6 can be transformed with hydroxylamine into the amidoxime functionality to extend peripheral structural diversity of 1,2,4-triazine derivatives.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the Operational Program Education for Competitiveness - ChemPharmNet (CZ.1.07/2.4.00/31.0130), IGA (IGA_PrF_2014011) and National Program of sustainability (project LO1304).

EXPERIMENTAL

All starting materials are commercially available. Commercial reagents were used without any purification. Melting points were determined with a Boetius stage apparatus and are uncorrected. Flash column chromatography was performed on silica gel (pore size 60 Å, 40–63 μm particle size). Purification of compounds via HPLC was performed with semipreparative HPLC (1200 Series, Agilent Technologies), column was YMC with following specifications: particle size 5 μm, inner diameter 20 mm, packing C18 (RP18, ODS, Octadecyl), Length 100 mm. Reactions were monitored by LC/MS analyses with a UHPLC-MS system consisting of a UHPLC chromatography Accela with photodiode array detector and triple quadrupole mass spectrometer TSQ Quantum Access (both Thermo Scientific, CA, USA), using a Nucleodur Gravity C18 column at 30 °C and flow rate of 800 mL/min (Kinetex, Phenomenex, 2.6 μm, 2.1 x 50 mm, USA). Mobile phase was (A; 0.01 M ammonium acetate in water) and (B; MeCN), linearly programmed from 10 to 80% B over 2.5 min, kept for 1.5 min. The column was reequilibrated with 10% B for 1 min. The APCI source operated at a discharge current of 5 mA, vaporizer temperature of 400 °C, and capillary temperature of 200 °C. High resolution mass spectrometer Exactive based on orbitrap mass analyser was equipped with Heated Electrospray Ionization (HESI). The spectrometer was tuned to obtain maximum response for *m/z* 70-700. The source parameters were set to the following values: HESI temperature 30 °C, spray voltage +3.5kV, -3kV; transfer capillary temperature 270 °C, sheath gas/aux gas (nitrogen) flow rates 35/10. The HRMS spectra of target peaks allowed evaluating their elemental composition with less than 3 ppm difference between experimental and theoretically calculated value. The ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 or $CDCl_3$ at 25 °C with a Varian 400 FT NMR or Jeol ECX-500SS spectrometer.

General methods for alkylation of triazine (1) via Mitsunobu reaction

Method A

Triphenylphosphine (0.197 g, 0.75 mmol) and DIAD (0.156 mL, 0.75 mmol) were dissolved in dry DCM (4 mL) and stirred for 5 min at rt. Subsequently, the corresponding aminoalcohol (**4**) (0.5 mmol) was added and the reaction mixture was stirred for the next 5 min, and finally, triazine (**1**) (0.107 mg, 0.5 mmol) was dissolved. The reaction mixture was stirred for 2.5 h at rt, then diluted with DCM (10 mL), and extracted with diluted (1M) HCl (3x5 mL). The collected water phase was alkalized with diluted ammonia (1:1) to pH~9 and a resulting mixture was extracted with DCM (3x5 mL). The DCM solution was washed with brine, dried with $MgSO_4$, and evaporated on a rotavap to dryness to provide a crude product which was purified on silica ($CHCl_3$:MeOH 10:1).

Method B

All reagents were mixed together as was described in Method A. Subsequently, after 1 h the additional portion of triphenylphosphine (0.197 g, 0.75 mmol) and DIAD (0.156 mL, 0.75 mmol) was added. The

reaction mixture was stirred for 2 h and then extracted with diluted (1M) HCl (4x5 mL). The collected water phase was alkalized with a saturated aqueous solution of sodium carbonate to pH~9 and extracted with EtOAc (3x20 mL). EtOAc solution was washed with brine, dried with $MgSO_4$, and evaporated on a rotovap to provide a crude product which was purified on silica ($CHCl_3$:MeOH 10:1).

Method C

Triphenylphosphine (0.197 g, 0.75 mmol) and DIAD (0.156 mL, 0.75 mmol) were dissolved in dry 1,4-dioxane (6 mL) and stirred for 5 min at rt. Subsequently, the corresponding aminoalcohol (**4**) (0.55 mmol) was added and the reaction mixture was stirred for the next 5 min. Finally, triazine (**1**) (0.107 mg, 0.5 mmol) was dissolved and the resulting reaction mixture was stirred at rt for 2 h. 1,4-Dioxane was evaporated on a rotovap to dryness to yield a crude product which was purified on silica ($CHCl_3$:MeOH 10:1 – 100:1, a mobile phase was chosen with respect to polarity of purified product).

Method D

Triazine (**1**) (53.5 mg, 0.25 mmol) and DIAD (0.078 mL, 0.375 mmol) were dissolved in dry 1,4-dioxane (6 mL). After that, polymer-bound triphenylphosphine (0.32g, 100-200 mesh, loading ~1.6 mmol/g) was added and the reaction mixture was stirred for 5 min. Finally, the corresponding alcohol (**4**) (0.275 mmol) was added and resulting mixture was stirred at rt for 2 h. Then the reaction mixture was filtrated, a solvent was evaporated on a rotovap to provide a crude product which was purified on silica ($CHCl_3$:MeOH 100:1).

4-(3-(Dimethylamino)propyl)-3,5-dioxo-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (5a): Following the **Method A**, the reaction was performed with alcohol (**4a**) (51.6 mg, 0.500 mmol) to yield (**5a**) as a yellow solid. (68.8 mg, 46%). Following the **Method C**, the reaction was performed with alcohol (**4a**) (56.7 mg, 0.550 mmol) to yield (**5a**) after purification on silica ($CHCl_3$:MeOH 10:1) as a yellow solid (89.7 mg, 60%); mp 88.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.5 (m, 5 H) 3.9 (t, J = 7.5 Hz, 2 H) 2.3 (t, J = 6.8 Hz, 2 H) 2.1 (s, 6 H) 1.7 (quin, J = 7.2 Hz, 2 H); ^{13}C NMR (101MHz, DMSO-d_6) δ ppm 153.9, 147.4, 139.7, 129.2, 129.0, 125.8, 121.3, 112.5, 56.3, 44.9, 39.7, 24.0; HRMS (HESI, *m/z*) calcd for $C_{15}H_{17}N_5O_2$ (299.14) $[M+H]^+$ 300.1455, found 300.1459.

3,5-Dioxo-2-phenyl-4-(3-(pyridin-4-yl)propyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (5c): Following the **Method B**, the reaction was performed with alcohol (**4c**) (68.6 mg, 0.500 mmol) to yield (**5c**) as a yellow solid (125.0 mg, 75%). Following the **Method C**, the reaction was performed with alcohol (**4c**) (75.4 mg, 0.550 mmol) to yield (**5c**) after purification on silica ($CHCl_3$:MeOH 10:1) as a yellow solid (141.6 mg, 85%); mp 109 °C; ^{1}H NMR (500MHz, DMSO-d_6) δ ppm 8.46 (d, J = 5.7 Hz, 2 H), 7.58 - 7.47 (m, 5 H), 7.26 (d, J = 6.3 Hz, 2 H), 3.87 (t, J = 7.2 Hz, 2 H), 2.70 (t, J = 7.7 Hz, 2 H), 1.94 (quin, J = 7.4 Hz, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 154.0, 150.1, 149.5, 147.4, 139.7, 129.2,

129.0, 125.8, 123.8, 121.4, 112.5, 40.8, 31.4, 26.6; HRMS (HESI, *m/z*) calcd for $C_{18}H_{15}N_5O_2$ (333.12) $[M+H]^+$ 334.1299, found 334.1299.

3,5-Dioxo-2-phenyl-4-(3-(pyridin-3-yl)propyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (5d): Following the **Method B**, the reaction was performed with alcohol (**4d**) (68.6 mg, 0.500 mmol) to yield (**5d**) as a yellow solid (91.7 mg, 55%). Following the **Method C**, the reaction was performed with alcohol (**4d**) (75.4 mg, 0.550 mmol) to yield (**5d**) after purification on silica ($CHCl_3$:MeOH 10:1) as a yellow solid (153.4 mg, 92%); mp 129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.5 (d, *J* = 2.2 Hz, 1 H) 8.4 (dd, *J* = 4.8, 1.8 Hz, 1 H) 7.7 (dt, *J* = 7.9, 2.0 Hz, 1 H) 7.5 (m, 5 H) 7.3 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1 H) 3.9 (t, *J* = 7.2 Hz, 2 H) 2.7 (t, *J* = 7.5 Hz, 1 H) 1.9 (quin, *J* = 7.5 Hz, 2 H); ^{13}C NMR (101MHz , DMSO-d_6) δ ppm 154.0, 149.6, 147.4, 147.3, 139.7, 136.6, 135.7, 129.2, 129.1, 125.8, 123.4, 121.4, 112.5, 40.8, 29.3, 27.5; HRMS (HESI, *m/z*) calcd for $C_{18}H_{15}N_5O_2$ (333.12) $[M+H]^+$ 334.1299, found 334.1297.

3,5-Dioxo-2-phenyl-4-(2-(pyridin-2-yl)ethyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (5f): Following the **Method B**, the reaction was performed with alcohol (**4f**) (61.6 mg, 0.500 mmol) to yield (**5f**) as a yellow solid (79.8 mg, 50%). Following the **Method C**, the reaction was performed with alcohol (**4f**) (67.7 mg, 0.550 mmol) to yield (**5f**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (127.7 mg, 80%). Following the **Method D**, the reaction was performed with alcohol (**4f**) (33.9 mg, 0.275 mmol) to yield (**5f**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (64.7 mg, 81%); mp 99 °C; ^{1}H NMR (400 MHz ,$CDCl_3$) δ ppm 8.50 (d, *J* = 4.8 Hz, 1 H), 7.63 (dt, *J* = 1.8, 7.7 Hz, 1 H), 7.53 - 7.41 (m, 5 H), 7.22 (d, *J* = 7.9 Hz, 1 H), 7.19 - 7.14 (m, 1 H), 4.43 (t, *J* = 7.2 Hz, 2 H), 3.19 (t, *J* = 7.2 Hz, 2 H); ^{13}C NMR (101 MHz ,$CDCl_3$) δ ppm 157.5, 152.8, 149.3, 146.9, 139.2, 136.8, 129.4, 129.2, 125.0, 123.5, 122.0, 121.6, 111.1, 41.7, 34.5; HRMS (HESI, *m/z*) calcd for $C_{17}H_{13}N_5O_2$ (319.11) $[M+H]^+$ 320.1142, found 320.1143.

4-(2-(1*H*-Imidazol-1-yl)propyl)-3,5-dioxo-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (5g): Following the **Method B**, the reaction was performed with alcohol (**4g**) (63.1 mg, 0.500 mmol) to yield (**5g**) as a yellow solid (74.1 mg, 46%). Following the **Method C**, the reaction was performed with alcohol (**4g**) (69.4 mg, 0.550 mmol) to yield (**5g**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (108.8 mg, 67%); mp 122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.64 (s, 1 H), 7.59 - 7.47 (m, 5 H), 7.19 (s, 1 H), 6.90 (br. s., 1 H), 4.06 (t, *J* = 7.2 Hz, 2 H), 3.84 (t, *J* = 6.9 Hz, 2 H), 2.07 (quin, *J* = 7.0 Hz, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 154.0, 147.4, 139.6, 137.2, 129.2, 129.1, 128.4, 125.7, 121.3, 119.2, 112.5, 43.7, 38.8, 27.9; HRMS (HESI, *m/z*) calcd for $C_{16}H_{14}N_6O_2$ (322.12) $[M+H]^+$ 323.1251, found 323.1249.

***tert*-Butyl (2-(6-cyano-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)-1-phenylethyl)carbamate (5h):** Following the **Method C**, the reaction was performed with alcohol (**4h**) (130.4 mg, 0.550 mmol) to

yield (**5h**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (130.0 mg, 60%); mp 194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.7 (d, J = 9.4 Hz, 1 H) 7.5 (m, 10 H) 5.1 (d, J = 3.9 Hz, 1 H) 4.3 (t, J = 12.1 Hz, 1 H) 4.0 (m, 1 H) 1.3 (s, 9 H)**;** ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 155.8, 153.7, 147.1, 139.4, 138.7, 129.4, 129.2, 128.5, 127.7, 126.9, 125.5, 121.1, 112.2, 78.4, 51.2, 46.1, 28.0; HRMS (HESI, *m/z*) calcd for $C_{23}H_{23}N_5O_4$ (433.18) $[M+H]^+$ 434.1823, found 434.1823.

***tert*-Butyl (3-(6-cyano-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)butyl)carbamate (5i):** Following the **Method C**, the reaction was performed with alcohol (**4i**) (104.1 mg, 0.550 mmol) to yield (**5i**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (134.9 mg, 70%); mp 141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.5 (m, 5 H) 6.9 (t, J = 5.5 Hz, 1 H) 3.8 (t, J = 7.5 Hz, 2 H) 3.0 (q, J = 6.6 Hz, 2 H) 1.7 (quin, J = 7.1 Hz, 2 H) 1.4 (s, 9 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 155.6, 153.9, 147.4, 139.7, 129.2, 129.0, 125.8, 121.4, 112.5, 77.6, 39.4, 37.6, 28.2, 26.8; HRMS (HESI, *m/z*) calcd for $C_{19}H_{23}N_5O_4$ (385.18) $[M+H]^+$ 386.1823, found 386.1822.

***tert*-Butyl (1-(6-cyano-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)-3-phenylpropan-2-yl)-carbamate (5j):** Following the **Method C**, the reaction was performed with alcohol (**4j**) (138.1 mg, 0.550 mmol) to yield (**5j**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (174.5 mg, 78%); mp 175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.4 - 7.6 (m, 5 H) 7.2 - 7.3 (m, 5 H) 7.1 (d, J = 8.8 Hz, 1 H) 4.1 - 4.2 (m, 1 H) 4.1 (dd, J = 12.7, 9.2 Hz, 1 H) 3.8 (dd, J = 12.5, 4.2 Hz, 1 H) 2.8 (dd, J = 14.0, 5.7 Hz, 1 H) 2.8 (dd, J = 14.0, 8.8 Hz, 1 H) 1.3 (s, 9 H); ^{13}C NMR (101 MHz , DMSO-d_6) δ ppm 156.3, 154.4, 147.7, 140.0, 138.9, 129.8, 129.6, 129.3, 128.7, 126.7, 126.0, 121.4, 112.7, 78.4, 49.1, 45.8, 37.4, 28.5; HRMS (HESI, *m/z*) calcd for $C_{24}H_{25}N_5O_4$ (447.19) $[M+H]^+$ 448.1979, found 448.1978.

***tert*-Butyl (1-(benzyloxy)-3-(6-cyano-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)propan-2-yl)carbamate (5k):** Following the **Method C**, the reaction was performed with alcohol (**4k**) (154.7 mg, 0.550 mmol) to yield (**5k**) after purification on silica ($CHCl_3$:MeOH 100:1) as a yellow solid (167.1 mg, 70%); mp 129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.5 (m, 5 H) 7.3 (m, 5 H) 7.0 (d, J = 8.8 Hz, 1 H) 4.5 (d, J = 5.7 Hz, 2 H) 4.1 (m, 1 H) 4.0 (m, 2 H) 3.5 (m, 2 H) 1.3 (s, 9 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 156.2, 154.4, 147.8, 140.0, 138.6, 129.8, 129.6, 128.7, 127.9, 127.9, 126.0, 121.4, 112.7, 78.6, 72.5, 70.1, 47.7, 28.5; HRMS (HESI, *m/z*) calcd for $C_{25}H_{27}N_5O_5$ (477.20) $[M+H]^+$ 478.2085, found 478.2086.

3,5-Dioxo-2-phenyl-4-(*p*-tolyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (7a): Triazine (**1**) (50 mg, 0.234 mmol) was dissolved in DMF (2 mL), then Cu_2O (33.5 mg, 0.234 mmol) and tolylboronic acid (**6a**) (127.3 mg, 0.936 mmol) were added. The reaction mixture was stirred under air atmosphere for 48 h and then Cu_2O was removed by filtration. To a filtrate saturated aqueous solution of $NaHCO_3$ (15 mL) was added and the mixture was extracted with EtOAc (3x15 mL). Collected organic phases were washed

with brine and dried with Na_2SO_4. The solvent was evaporated on a rotovap to give a crude product which was purified on silica ($CHCl_3$) and then on semi preparative chromatography as a beige solid (39.2 mg, 55%); mp 78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.55 - 7.44 (m, 5 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 2.41 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 152.9, 147.1, 140.5, 139.3, 130.6, 129.6, 129.3, 129.1, 127.2, 125.1, 122.5, 111.2, 21.4; HRMS (HESI, *m/z*) calcd for $C_{17}H_{12}N_4O_2$ (304.10) $[M+H]^+$ 305.1033, found 305.1033.

4-(4-Methoxyphenyl)-3,5-dioxo-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (7b): Following the procedure for (**7a**), the reaction was performed with (**6b**) (142.2 mg, 0.936 mmol) to afford (**7b**) as a beige solid (41.9 mg, 56%); mp 190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.54 - 7.44 (m, 5 H), 7.20 (d, *J* = 9.2 Hz, 2 H), 7.03 (d, *J* = 9.2 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 160.6, 153.0, 147.3, 139.2, 129.6, 129.3, 128.7, 125.1, 124.0, 122.5, 115.2, 111.1, 55.7; HRMS (HESI, *m/z*) calcd for $C_{17}H_{12}N_4O_3$ (320.09) $[M+H]^+$ 321.0982, found 321.0982.

3,5-Dioxo-2,4-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (7c): Following the procedure for (**7a**), the reaction was performed with (**6c**) (114.1 mg, 0.936 mmol) to afford (**7c**) as a beige solid (38.0 mg, 56%); mp 187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.58 - 7.42 (m, 8 H), 7.29 (d, *J* = 6.9 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 152.8, 147.0, 139.3, 131.7, 130.2, 129.9, 129.6, 129.3, 127.6, 125.1, 122.6, 111.1; HRMS (HESI, *m/z*) calcd for $C_{16}H_{10}N_4O_2$ (290.08) $[M+H]^+$ 291.0877, found 291.0876.

***tert*-Butyl (2-(6-(*N*'-hydroxycarbamimidoyl)-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)-1-phenylethyl)carbamate (8h):** Alkylated triazine (**5h**) (70.0 mg, 0.21 mmol) was dissolved in dry EtOH (2 mL) and afterwards $NH_2OH{\cdot}HCl$ (29.2 mg, 0.42 mmol) was added. Then a solution of NH_3/EtOH (0.38 mL, 4.2 mmol) diluted with dry EtOH (3.8 mL) was poured into the reaction vessel and the mixture was stirred at rt for 4 h. After the reaction was finished, the EtOH was evaporated on a rotovap, water was added (10 mL) and the resulting precipitate was removed by filtration and dried in the vacuum drier as a yellow solid (**8h)** with yield (43.7 mg, 58%); mp 220 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ ppm 10.14 (s, 1 H), 7.63 - 7.18 (m, 10 H), 5.64 (br. s., 2 H), 5.11 (d, *J* = 14.9 Hz, 1 H), 4.25 (t, *J* = 12.6 Hz, 1 H), 3.98 (dd, *J* = 5.2, 13.2 Hz, 1 H), 1.31 (s, 9 H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ ppm 156.0, 154.1, 148.3, 146.6, 140.7, 140.1, 136.1, 129.3, 128.9, 128.7, 128.0, 127.4, 125.9, 78.7, 51.9, 46.1, 28.6; HRMS (HESI, *m/z*) calcd for $C_{23}H_{26}N_6O_5$ (466.20) $[M+H]^+$ 467.2037, found 467.2024.

***tert*-Butyl (1-(6-(*N*'-hydroxycarbamimidoyl)-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)-3-phenylpropan-2-yl)carbamate (8j):** Following the procedure for (**8h**), the reaction was performed with (**5j**) (73 mg, 0.21 mmol) to yield (**8j**) as a yellow solid (50.9 mg, 65%); mp 228 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ ppm 10.11 (s, 1 H), 7.55 - 7.16 (m, 10 H), 6.90 (d, *J* = 9.2 Hz, 1 H), 5.60 (s, 2 H),

4.25 - 4.15 (m, 1 H), 4.08 (dd, *J* = 9.7, 12.6 Hz, 1 H), 3.84 - 3.76 (m, 1 H), 2.84 - 2.76 (m, 2 H), 1.23 (s, 9 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 156.1, 154.5, 148.5, 146.8, 140.9, 139.2, 136.1, 129.4, 129.2, 128.7, 128.6, 126.6, 126.0, 78.2, 49.2, 45.3, 37.9, 28.6; HRMS (HESI, *m/z*) calcd for $C_{24}H_{28}N_6O_5$ (480.22) $[M+H]^+$ 481.2194, found 481.2189.

***tert*-Butyl (1-(benzyloxy)-3-(6-(*N'*-hydroxycarbamimidoyl)-3,5-dioxo-2-phenyl-2,3-dihydro-1,2,4-triazin-4(5*H*)-yl)propan-2-yl)carbamate (8k):** Following the procedure for (**8h**), the reaction was performed with (**5k**) (79.3 mg, 0.21 mmol) to yield (**8k**) as a yellow solid (52.6 mg, 62%); mp 181 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.12 (s, 1 H), 7.56 - 7.24 (m, 10 H), 6.80 (d, *J* = 9.2 Hz, 1 H), 5.62 (s, 2 H), 4.48 (t, *J* = 12.0 Hz, 2 H), 4.24 - 4.14 (m, 1 H), 4.06 - 3.91 (m, 2 H), 3.56 - 3.45 (m, *J* = 6.3 Hz, 2 H), 1.30 (s, 9 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 156.1, 154.5, 148.5, 146.8, 140.8, 138.7, 136.1, 129.2, 128.8, 128.6, 128.0, 126.0, 78.5, 72.5, 70.6, 47.7, 43.0, 28.6; HRMS (HESI, *m/z*) calcd for $C_{25}H_{30}N_6O_6$ (510.23) $[M+H]^+$ 511.2300, found 511.2294.

REFERENCES

1. J. B. Hobbs, *Comprehensive Medicinal Chemistry*, 1990, **2**, 299; J. L. Davis and J. L. Gookin, *Veterinary Pharmacology and Therapeutics*, 2009, 1145; D. Reines, *Methods in Enzymology*, 2003, **371**, 284.
2. H. Xu, U.S. Pat. Appl. Publ. 2013, US 20130252958 A1 20130926.
3. Z. Rankovic, J. Cai, X. Fradera, M. Dempster, A. Mistry, A. Mitchell, C. Long, E. Hamilton, A. King, S. Boucharens, C. Jamieson, J. Gillespie, I. Cumming, J. Uitdehaag, and M. van Zeeland, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1488.
4. E. Riguet, B. Campo, A. Gibelin, and K. Mhalla, PCT Int. Appl. Patent 2008, WO 2008056257 A2 20080515.
5. A. J. Duplantier, M. A. Dombroski, C. Subramanyam, B. A. Beaulieu, S. Chang, C. A. Gabel, C. Jordan, A. S. Kalgutkar, K. G. Kraus, J. M. Labasi, C. Mussari, D. G. Perregaux, R. Shepard, T. J. Taylor, K. A. Trevena, C. Whitney-Pickett, and K. Yoon, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3708.
6. J. Pontillo, Z. Guo, D. Wu, R. S. Struthers, and C. Chen, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4363.
7. J. Slouka, *Monatsh. Chem.*, 1968, **99,** 1808.
8. D. Banerjee, K. Junge, and M. Beller, *Angew. Chem. Int. Ed.*, 2014, **53**, 1630.
9. V. Gembus, F. Marsais, and V. Levacher, *Synlett*, 2008, **10**, 1463; J. Cieslak and S. L. Beaucage, *J. Org. Chem.*, 2003, **68**, 10123; D. Morisaki, H.-S. Kim, H. Inoue, H. Terauchi, S. Kuge, A. Naganuma, Y. Wataya, H. Tokuyama, M. Ihara, and K. Takasu, *Chem. Sci.*, 2010, **1**, 206; J. L. Wong, M. S. Brown, and H. Rapoport, *J. Org. Chem.*, 1965, **30**, 2398.
10. J. X. Qiao and P. Y. S. Lam, *Synthesis*, 2011, 829; K. S. Rao and T.-S. Wu, *Tetrahedron*, 2012, **68**,

7735.

11. B. Sreedhar, G. T. Venkanna, K. B. S. Kumar, and V. Balasubrahmanyam, *Synthesis*, 2008, 795.
12. P. Cankar and J. Slouka, *Acta Univ. Palacki. Olomuc., Fac. Rerum Nat., Chem*, 2000, **39**, 15.