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Anton V. Dolzhenko,[1] Wai-Keung Chui[1] and Anna V. Dolzhenko[2]

Synthesis of fused 2-amino-4-oxo-1,3,5-triazines *via* microwave-assisted ring closure carbonylation of azahetarylguanidines

[1]Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore.

[2]Perm State Pharmaceutical Academy, 48 Lenin Street, Perm 614990, Russian Federation.

phada@nus.edu.sg, avdolzh@inbox.ru

Abstract

The microwave-assisted ring closure of 2-benzoxazolylguanidines (**1a-c**), 2-benzothiazolylguanidines (**3a-c**) and 2-benzimidazolylguanidine (**5**) using phenyl isocyanate as a carbonylating reagent afforded 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**), 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole (**4a-c**) and 2-amino-4-oxo-3*H*-[1,3,5]triazino[1,2-*a*]benzimidazole (**6**), respectively. The tautomerism in the prepared compounds was investigated. Compounds **2a-c** and **4a-c** were found to exist in DMSO solution as 2-imino-4-oxo-tautomers. 2-Amino-4-oxo-3*H*- and 2-amino-4-hydroxy- forms of **6** predominated in tautomeric equilibrium at the same condition.

Key words: hetarylguanidines, carbonylation, microwave irradiation, fused 1,3,5-triazines, phenyl isocyanate, tautomerism.

Introduction

The use of microwave irradiation has found extensive applications in the synthesis of heterocyclic compounds [1-4]. However microwave-assisted annelation of the 1,3,5-triazine ring to a heterocyclic scaffold has not yet been reported.

Ring closure carbonylation of the azahetarylguanidines with the formation of 2-amino-4-oxo-1,3,5-triazines can be achieved by using several reagents. Thus the syntheses of 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzoxazole and 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole have been reported using conventional heating of 2-benzoxazolylguanidine (**1a**) or 2-benzothiazolylguanidine (**3a**) with diethyl azodicarboxilate [5,6] or tosyl isocyanates [7]. In the literature, a number of reagents such as diethyl azodicarboxilate [5,6], benzoyl isocyanate, carbethoxy isocyanate, carbethoxy isothiocyanate [8], diethyl carbonate or diphenyl carbonate [9,10] have been applied for 1,3,5-triazine ring annelation to the benzimidazole skeleton *via* carbonylation of 2-benzimidazolylguanidine (**5**).

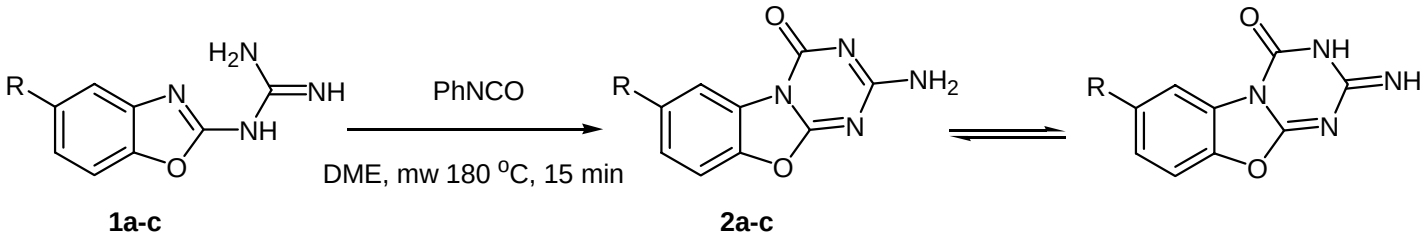
Herein we report microwave-assisted ring closure carbonylation of azahetarylguanidines, namely 2-benzoxazolylguanidines (**1a-c**), 2-benzothiazolylguanidines (**3a-c**) and 2-benzimidazolylguanidine (**5**) with the formation of 2-amino-4-oxo-1,3,5-triazine fused with benzoxazole, benzothiazole and benzimidazole heterocyclic nuclei, respectively.

Tautomerism in heterocycles has been a subject of investigation [11-14] because tautomerism plays an important role in chemical reactions as well as biological activities. The target molecules have a tendency to exhibit tautomerism as such we have decided also to investigate this phenomenon by using spectral analysis.

Results and discussion

Microwave-assisted reaction of **1a-c** with phenyl isocyanate led to the formation of 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**) (Scheme 1). The reactions effectively proceeded at 180 °C in 1,2-dimethoxyethane (DME) and afforded compounds (**2a-c**) with high yield and purity (Table 1).

Scheme 1

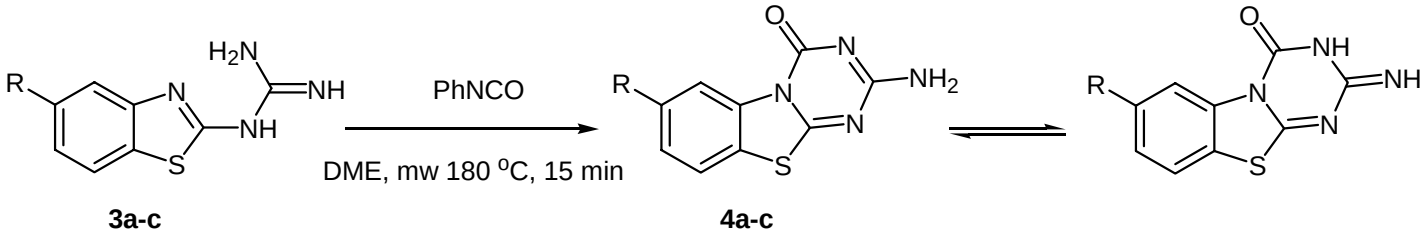


1a-c **2a-c**

1,2a R = H,
1,2b R = Me,
1,2c R = Cl

The ring closure carbonylation of 2-benzothiazolylguanidines (**3a-c**) was successfully achieved under microwave irradiation using phenyl isocyanate (Scheme 2). Thus 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzothiazoles (**4a-c**) were also prepared with good yields (Table 1) under the same reaction conditions.

Scheme 2



3a-c **4a-c**

3,4a R = H,
3,4b R = Cl,
3,4c R = CF_3

Reaction of 2-benzimidazolylguanidine (**5**) with phenyl isocyanate under microwave irradiation proceeded with the formation of 2-amino-4-oxo-3*H*-[1,3,5]triazino[1,2-*a*]benzimidazole (**6**) (Scheme 3). It has been reported that the reaction of **5** with phenyl isocyanate in pyridine under reflux afforded N-[(1H-benzimidazol-2-ylamino)(imino)methyl]-N'-phenylurea [9] insted. Therefore it seems to be likely that microwave irradiation can facilitate elimination of aniline from the intermediate adduct with the formation of **6**.

Scheme 3

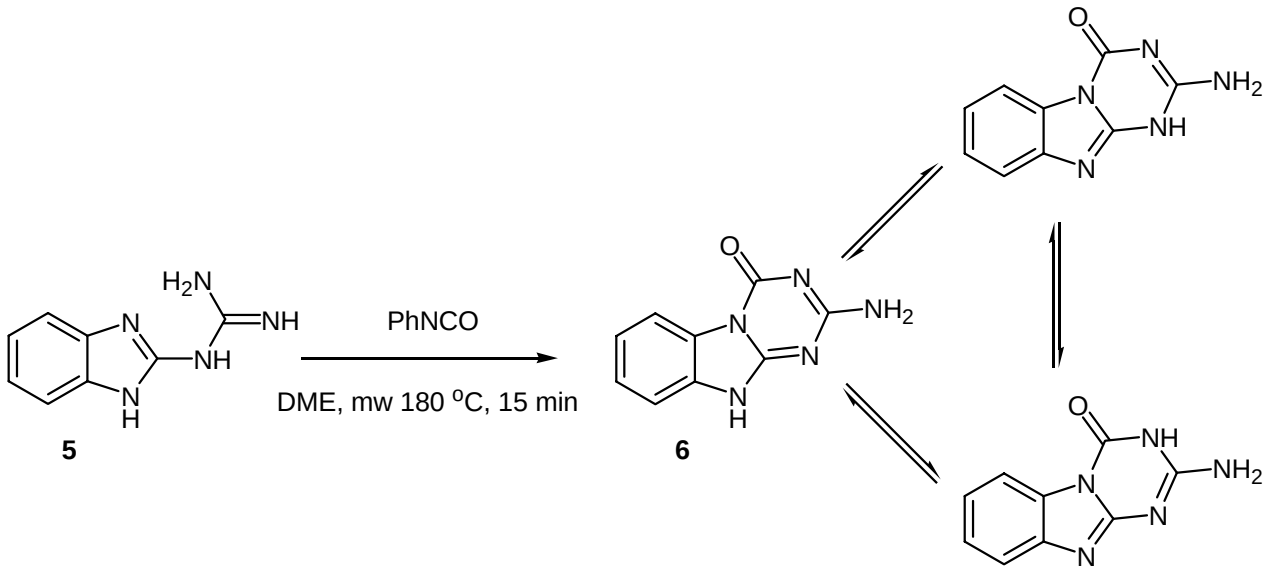


Table 1

Physicochemical characteristics of 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**), 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzothiazoles (**4a-c**) and 2-amino-4-oxo-3*H*-[1,3,5]triazino[1,2-*a*]benzimidazole (**6**)

Compound	R	Molecular Formula*	Yield (%)	Mp (°C)	IR (KBr), ν (cm^{-1})
2a	H	$C_9H_6N_4O_2$ (202.2)	90	>360	3359 (NH), 3075 (NH), 1703 (C=O), 1691, 1666, 1472, 1440, 1077, 760
2b	Me	$C_{10}H_8N_4O_2$ (216.2)	92	293-295	3372 (NH), 3318 (NH), 3191 (NH), 3034, 1705 (C=O), 1668, 1651, 1486, 1439, 1074, 782
2c	Cl	$C_9H_5ClN_4O_2$ (236.6)	90	298	3266 (NH), 3081(NH), 1741, 1728, 1473, 1436, 1085, 776, 667
4a	H	$C_9H_6N_4OS$ (218.2)	96	343-344	3332 (NH), 3107 (NH), 1722, 1702, 1648, 1554, 1507, 1455, 1428, 1112, 779, 758, 636
4b	Cl	$C_9H_5ClN_4OS$ (252.7)	90	>360	3306 (NH), 3108 (NH), 1721, 1699, 1674, 1578, 1565, 1510, 1469, 1455, 1438, 1226, 1120, 799, 768, 636
4c	CF_3	$C_{10}H_5F_3N_4OS$ (286.2)	95	324	3283 (NH), 3123 (NH), 1713 (C=O), 1652, 1609, 1561, 1513, 1442, 1334, 1249, 1126, 776, 734, 663
6	H	$C_9H_7N_5O$ (201.2)	95	>360	3415 (NH), 3219 (NH), 3123 (NH), 2997, 2886, 2800, 1717 (C=O), 1616, 1601, 1526, 1457, 1405, 774, 736

* Satisfactory elemental analyses were obtained.

The prepared compounds (**2a-c**, **4a-c**, **6**) were fully characterized according to the analytical and spectroscopic properties (Tables 1-3).

The anisotropic effect of the oxygen atom led to the downfield shift of the signal of H-6 to 7.90-7.98, 8.62-8.91 and 8.09 ppm in the ^{1}H NMR spectra (Table 2) of 1,3,5-triazino[2,1-*b*][1,3]benzoxazole (**2a-c**), 1,3,5-triazino[2,1-*b*][1,3]benzothiazole (**4a-c**) and 1,3,5-triazino[1,2-*a*]benzimidazole (**6**) derivatives, respectively. These findings confirmed the 1,3,5-triazine ring formation.

The signals at 162.9-166.0 ppm in the ^{13}C NMR spectra (Table 3) confirmed the presence of the carbonyl group in the structures of compounds **2a-c**, **4a-c** and **6**.

Table 2

^{1}H NMR spectral data for 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**), 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzothiazoles (**4a-c**) and 2-amino-4-oxo-3*H*-[1,3,5]triazino[1,2-*a*]benzimidazole (**6**) (300 MHz, DMSO-d_6/TMS, δ, ppm)

Compound	H-6	H-7 (R)	H-8	H-9	2NH / NH_2
2a	7.98 dd, *J* = 7.2, 1.5 Hz	7.46 td, *J* = 7.2, 1.9 Hz	7.44 td, *J* = 7.2, 1.5 Hz	7.71 dd, *J* = 7.2, 1.9 Hz	7.78 and 7.80, two s, 2NH
2b	7.78 s	2.43 s, 3H, Me	7.22 dd, *J* = 8.3, 1.1 Hz	7.56 d, *J* = 8.3 Hz	7.75 and 7.76, two s, 2NH
2c	7.90 d, *J* = 2.3 Hz	-	7.49 dd, *J* = 8.7, 2.3 Hz	7.75 d, *J* = 8.7 Hz	7.86 and 7.87, two s, 2NH
4a	8.63 dd, *J* = 7.9, 1.1 Hz	7.54 td, *J* = 7.7, 1.1 Hz	7.46 td, *J* = 7.5, 1.1 Hz	7.98 dd, *J* = 7.7, 1.1 Hz	7.63 and 7.70, two s, 2NH
4b	8.62 d, *J* = 2.2 Hz	-	7.54 dd, *J* = 8.3, 2.2 Hz	8.01 d, *J* = 8.3 Hz	7.70 and 7.76, two s, 2NH
4c	8.91 d, *J* = 1.1 Hz	-	7.82 dd, *J* = 8.3, 1.1 Hz	8.23 d, *J* = 8.3 Hz	7.71 and 7.78, two s, 2NH
6	8.09 d, *J* = 7.5 Hz	7.34 td, *J* = 7.7, 1.5 Hz	7.25 td, *J* = 7.7, 1.1 Hz	7.42 d, *J* = 7.2 Hz	7.19 br. s, 2H, NH_2 12.20 br. s, 1H, NH

Two potentially tautomeric groups are present in compounds **2a-c**, **4a-c** and **6**. Thus amino-imino group tautomerism at position 2 and oxo-hydroxy group tautomerism at position 4 of the heterocycles **2a-c**, **4a-c** and **6** are possible theoretically. However the tautomerization of 4-oxo group is not favorable for 1,3,5-triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**) and 1,3,5-triazino[2,1-*b*][1,3]benzothiazoles (**4a-c**). The amino-imino tautomerism was found to take place in the benzoxazole (**2a-c**) and benzothiazole (**4a-c**) derivatives. Thus 1,3,5-triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**) and 1,3,5-triazino[2,1-*b*][1,3]benzothiazoles (**4a-c**) existed in DMSO at 25 ºC as the

imino tautomeric forms. This was supported by the evidence of two defined D_2O exchangeable singlets at 7.63-7.87 ppm in the ^{1}H NMR spectra which belonged to N(3)*H* and the imino group of **3a-c** and **4a-c**.

Table 3

^{13}C NMR spectral data for 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzoxazoles (**2a-c**), 2-amino-4-oxo-[1,3,5]triazino[2,1-*b*][1,3]benzothiazoles (**4a-c**) and 2-amino-4-oxo-3*H*-[1,3,5]triazino[1,2-*a*]benzimidazole (**6**) (75 MHz, DMSO-d_6/TMS, δ, ppm)

Compd.	C-2	C-4	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a	R
2a	151.1	166.0	126.0	111.0	125.3*	125.5*	114.0	143.4	161.3	-
2b	151.0	165.9	125.9	110.5	135.0	125.8	114.2	141.5	161.4	Me 20.9
2c	150.7	165.9	127.3	112.5	129.2	125.2	113.6	142.4	161.6	-
4a	151.6	163.5	121.6	117.7	127.0	125.9	122.9	135.7	170.2	-
4b	151.3	163.5	120.7	117.2	131.5	125.8	124.4	136.6	170.5	-
4c	151.5	163.5	126.9	113.9	127.3	122.4	124.2	136.1	170.4	CF_3 123.9
			J = 1.2 Hz	*J* = 4.5 Hz	*J* = 32.1 Hz	*J* = 3.7 Hz				*J* = 272.6 Hz
6	150.3	162.9	126.6	112.6	121.8	124.7	113.9	133.1	153.7	-

* - Assignments may be reversed.

The broad signal of two protons at 7.19 ppm was observed in ^{1}H NMR spectrum of 1,3,5-triazino[1,2-a]benzimidazole (**6**) and assigned to the amino group. However three 1*H*-, 3*H*- and 10*H*- tautomeric forms (Scheme 3) are possible for **6** considering annular tautomerism in this compound. The downfield shift and broadening of the signal of annular NH proton in ^{1}H NMR spectrum of compound **6** together with broadening of the signals of C-2, C-4, C-5a, C-6 and C-9a in ^{13}C NMR spectrum of the same compound indicated the presence in the tautomeric equilibrium 4-hydroxy form (Figure 1) and predominance of 3*H*- form in annular tautomerism. At the same time according to IR spectrum (Table 1) compound **6** in solid state existed as 4-oxo form.

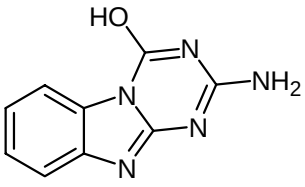


Figure 1

2-Amino-4-hydroxo-[1,3,5]triazino[1,2-a]benzimidazole – one of the tautomeric form of compound **6**

Experimental

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were performed on a Jasco FT-IR-430 spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-d_6 as a solvent and TMS as an internal reference. Microwave-assisted syntheses were carried out using microwave synthesizer Initiator^{TM} (Biotage AB, Sweden).

General procedure for the ring closure carbonylation of 2-benzoxazolylguanidines, 2-benzothiazolylguanidines and 2-benzimidazolylguanidine:

The mixtures of hetarylguanidine (**1a-c**, **3a-c** or **5** 5 mmol) and phenyl isocyanate (5 mmol) in 5 mL DME were heated at 180 °C under microwave irradiation for 15 min. After cooling, precipitate of the target compound was filtered, washed with DME and dried. The compounds prepared in this manner were sufficiently pure, however they could be recrystallized from DMF (**2a-c**, **4a-c**) or DMSO (**6**).

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