Cyclocondensation Reactions of Heterocyclic Carbonyl Compounds V:[#] Synthesis of some 3-oxo-3,4-dihydro-1,2,4-triazino[2,3-*a*]benzimidazole-2-carbonitriles and their 4-methylderivatives

Petr Bílek*, Jan Slouka

Department of Organic Chemistry, Palacky University, 771 46 Olomouc, Czech Republic
E-mail: bilek@risc.upol.cz

Abstract

Cyclocondensation of some 1-(o-aminophenyl)-6-azauracil-5-carbonitriles **4a-4c** and their 3-methyl-derivatives **5a-5c** to the corresponding 3-oxo-3,4-dihydro-1,2,4-triazino[2,3-a]benzimidazole-2-carbonitriles **6a-6c** and their 4-methylderivatives **8a-8c** was studied. 17 new compounds were thus prepared, their characterization by m.p., C,H,N analysis and IR and NMR spectra is given.

Introduction

Contrary to the previous communication (**1**), where synthesis of some condensed 1,2,4-triazines based on cyclocondensation of a carbonyl group in position 4 of 6-azauracile ring was described, we are concerned with analogous condensation of an amino group with a carbonyl group in position 2 in this communication. Cyclocondensation of this kind has been used up to now merely for synthesis of some 1,2,4-triazino[2,3-*a*]quinazoline derivatives (**2**) and a few derivatives of 1,2,4-triazino[2,3-a]benzimidazole (**3**). The main aim of this communication is, therefore, more detailed investigation of the last cyclocondensation mentioned above.

Results

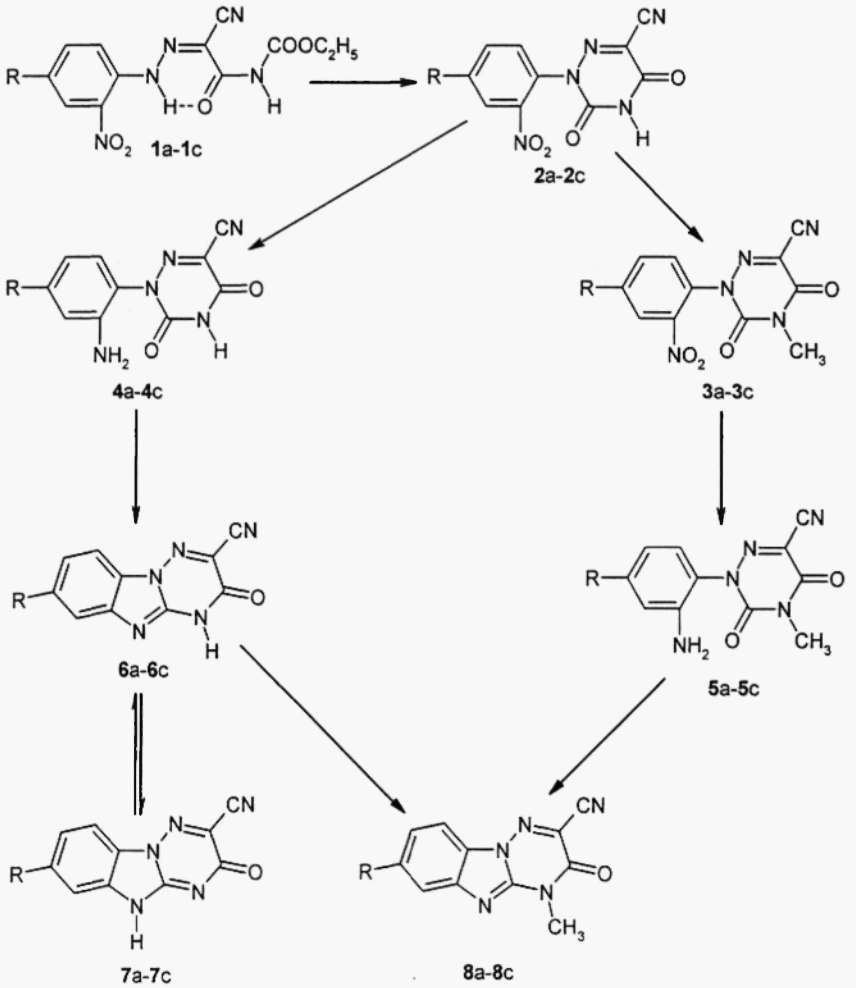
Diazotation of 4-substituted 2-nitroanilines and further coupling of formed diazonium salts with ethyl cyanoacetylcarbamate afforded hydrazones **1a-1c** in good yield. In the next step these hydrazones were cyclised to the substituted 1-(2-nitrophenyl)-6-azauracil-5-carbonitriles **2a-2c**. This cyclisation was carried out by natrium carbonate at room temperature and by boiling in xylene or anisole. Compounds **2** were converted into the corresponding 3-methylderivatives **3a-3c** by methylation with methyl iodide in basic solution. Nitrocompounds **2** and **3** were reduced by ferrous hydroxide to the appropriate aminoderivatives **4a-4c** and **5a-5c**. These compounds served for further study of their cyclocondensation to the corresponding 1,2,4-triazino[2,3-a]benzimidazole derivatives **6-8**. In this respect the most interesting was the question how methylation of the 6-azauracile ring can influence the course of the reaction. We observed in case of the non-methylated derivatives of 6-azauracile **4a-4c** that cyclocondensation proceeds smoothly already after

[#] Part IV: see ref. **1**

10 hours boiling in acetic acid or by 24 hours boiling in anisole. In case of the methylated derivatives **5a-5c** cyclocondensation proceeds slowly – in acetic acid about twice and in anisole proceeds only under acid catalysis (e.g. p-toluenesulfonic acid). In the absence of the acid catalyst the reaction didn't take place even after 100 hours boiling.

Cyclocondensation products of compounds **4** are 7-substituted 3-oxo-3,4-dihydro-1,2,4-triazino[2,3-a] benzimidazole-2-carbonitriles **6a-6c,** which are tautomeric with their 3,5-dihydro derivatives **7a-7c**. It can be assumed that the transformation of these tautomers is very fast due to the fast moving of hydrogen atoms.

In this connection the question of methylation of the mentioned condensed heterocycles was of interest, too. It may proceed on nitrogen in the position 4 (this would be according with methylation of tautomer form **6**) or on nitrogen 5 (this would be according with methylation of tautomer form **7**). We found that methylation by methyl iodide under basic conditions leads exclusively to the compounds identical with substances obtained by cyclocondensation of N-methyl-6-azauracils **5**, so that methylation proceeds in position 4 with formation of compounds **8**.



a) R=H b) R=CH_3 c) R=OCH_3

Apparatus and methods

The melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra were measured using KBr disc technique and scanned on an ATI Unicam Genesis FTIR instrument. Elemental analyses were performed by using an EA 1108 Elemental Analyser (Fison Instrument). NMR spectra were measured on a Bruker AMX-360 spectrometer (360 MHz) in DMSO-d_6 ; the chemical shifts δ are reported in ppm and coupling constants are in Hertz.

Experimental

Ethyl arylhydrazonocyanoacetyl carbamates **(1a-1c)**

General procedure:

Hydrochloric acid (37%, 3.5 ml) was added to a solution of corresponding amine (2-nitroaniline, 2-nitro-4-methylaniline or 2-nitro-4-methoxyaniline) (5 mmol) in acetic acid (98%, 20 ml) and water (3 ml). A solution of $NaNO_2$ (350 mg, 5.07 mmol) in ice-cold water (1.5 ml) was added dropwise at 0-5 °C. After 20 minutes the solution of diazonium salt was added to a pre-cooled solution of ethyl cyanoacetylcarbamate (1.05g, 6.1 mmol) and sodium acetate (22g) in water (350 ml). The reaction mixture was left to stand at 0-5 °C. The next day the precipitated solid was collected by suction, thoroughly washed with water and dried in air.

For further details, see tables **1** and **2**.

2-Aryl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitriles **(2a-2c)**

General procedures:

a) thermic cyclisation in xylene

A solution of corresponding hydrazone **1a-1c** (0.5 mmol) in xylene (25 ml) was refluxed 50 hours. Then the reaction mixture was concentrated to a small volume (about 5 ml) and cooled. The next day the precipitated solid was collected with suction, washed with little benzene and dried in air.

b) thermic cyclisation in anisole

A solution of **1a** (0.5 mmol) in anisole (15 ml) was refluxed 48 hours and then taken down *in vacuo*. The solid was mixed with little water and then collected with suction, washed with water and dried in air.

c) cyclisation in basic solution

A solution of corresponding hydrazone **1a-1c** (0.5 mmol) and Na_2CO_3 (120 mg, 1.13 mmol) in water (15 ml) was left to stand at room temperature with intermittent stirring for 12 days. Then the reaction mixture was filtered with charcoal and the filtrate was slowly acidified with diluted HCl (1:5) to pH 1-2. The precipitated solid was collected with suction, washed with water and dried on air.

The compounds were purified by recrystallisation from ethanol/water (1:1).

For further details, see tables **1** and **2**.

2-Aryl-3,5-dioxo-4-methyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitriles **(3a-3c)**

General procedure:

Redistilled methyl iodide (1.0 ml) was added to a solution of corresponding triazine **2a-2c** (1 mmol) and Na_2CO_3 (58 mg, 0.55 mmol) in 10-15 ml water. A firmly stoppered flask with the mixture was allowed to stand with intermittent stirring for 14 days. The excess of methyl iodide was removed under low pressure and the precipitated solid was collected with suction, washed with water and dried in air.

For further details, see tables **1** and 2.

2-(2-Amino-4-subst. phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitriles **(4a-4c)**

General procedure:

A solution of $FeSO_4.7H_2O$ (2.225 g, 8 mmol) in water (8 ml) was added to a warm solution of $Ba(OH)_2.8H_2O$ (2.525 g, 8 mmol) in water (18 ml). The mixture of precipitated $Fe(OH)_2$ and $BaSO_4$ was added in small portions to the solution of the corresponding nitro compound **2a-2c** (1 mmol) and ammonia (25%, 0.4 ml) in water (7 ml). Then the reaction mixture was heated at 60 °C for 5 minutes and on a boiling water bath for 60 minutes with stirring. The hot reaction mixture was filtered and the precipitate was thoroughly washed with 1% ammonia. Combined filtrates were taken down *in vacuo*. The solid was mixed with a small amount of water, ammonia and charcoal and filtered. The filtrate was carefully acidified with diluted HCl (1:5) to pH 5-6. The next day the precipitated solid was collected with suction, washed with water and dried in air.

The compounds were purified by recrystallisation from water.

For further details, see tables **1** and 2.

2-(2-Amino-4-subst. phenyl)-3,5-dioxo-4-methyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitriles **(5a-5c)**

General procedure:

A solution of $FeSO_4.7H_2O$ (1.39 g, 5 mmol) in water (7 ml) was added to a warm solution of $Ba(OH)_2.8H_2O$ (1.58 g, 5 mmol) in water (15 ml). The precipitated solid was quickly collected with suction and washed with ethanol. Then it was added in small portions to the stirred solution of the corresponding nitro compound **3a-3c** (0.5 mmol) in warm ethanol (20 ml). The mixture was refluxed 90 minutes on a hot water bath. Then the reaction mixture was filtered and the precipitate was washed with hot ethanol. Combined filtrates were taken down *in vacuo*. The solid was mixed with little water and after a few hours was collected with suction, washed with water and dried in air.

The compounds were purified by recrystallisation from ethanol.

For further details, see tables **1** and 2.

7-Subst.-3-oxo-3,4-dihydro-1,2,4-triazino[2,3-a]benzimidazole-2-carbonitriles **(6a-6c)**

General procedures:

a) cyclisation in acetic acid

A solution of corresponding amine **4a-4c** (1 mmol) in acetic acid (18 ml) was refluxed for 10 hours and then taken down. The solid was mixed with little water and after a few hours the precipitated solid was collected with suction, washed with water and dried in air.

b) cyclisation in anisole:

A solution of **4a** (1 mmol) in anisole (25 ml) was refluxed for 24 hours and then taken down *in vacuo*. The solid was mixed with little water and after a few hours the precipitated solid was collected with suction, washed with water and dried in air.

The compounds were purified by recrystallisation from concentrated acetic acid.

For further details, see tables **1** and **2**.

7-Subst.-3-oxo-4-methyl-3,4-dihydro-1,2,4-triazino[2,3-a]benzimidazole-2-carbonitriles **(8a-8c)**

General procedures:

a) methylation of **6a-6c**

Redistilled methyl iodide (1.0 ml) was added to the solution of the corresponding compound **6a-6c** (1 mmol) and Na_2CO_3 (58 mg) in water (35ml). A firmly stoppered flask with the mixture was allowed to stand with intermittent stirring for 14 days. The excess of methyl iodide was removed under low pressure and the precipitated solid was collected with suction, washed with water and dried in air.

b) thermic cyclisation in acetic acid

A solution of corresponding amine **5a-5c** (1 mmol) in acetic acid (30 ml) was refluxed for 12 hours and concentrated to a small volume (10 ml). After a few hours the precipitated solid was collected with suction, washed with water and dried in air.

c) thermic cyclisation in anisole

A solution of **5a** (1 mmol) and p-toluenesulfonic acid (120 mg) in anisole (25 ml) was refluxed for 4 hours and then taken down *in vacuo*. The solid was mixed with little water and after a few hours the precipitated solid was collected with suction, washed with water and dried in air.

The compounds were purified by recrystallisation from acetic acid.

For further details, see tables **1** and **2**.

Acknowledgment

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Table 1
Characteristic data of compounds 1-8

Compound	M.p. (°C) Yield (%)	Formula M.w.	Elemental analysis (Calculated/Found) % C	 % H	 % N	ν(C=O) cm^{-1}	ν(CN) cm^{-1}
1a	see ref. (**3**)	$C_{12}H_{11}N_5O_5$ 305.3					
1b	161-165 84.6	$C_{13}H_{13}N_5O_5$ 319.2	48.90 49.05	4.07 3.91	21.94 21.60	1763 1720	2216
1c	175-178 97.3	$C_{13}H_{13}N_5O_6$ 335.0	46.56 46.68	3.88 3.99	20.89 20.81	1774 1720	2221
2a	see ref. (**3**) 68.2[a];84.5[b]	$C_{10}H_5N_5O_4$ 259.2					
2b	233-235 62.3[a];81.1[c]	$C_{11}H_7N_5O_4$ 273.2	48.35 48.67	2.56 2.47	25.64 25.35	1753 1739	2247
2c	254-256 64.2[a];86.6[c]	$C_{11}H_7N_5O_5$ 289.4	45.67 45.65	2.42 2.51	24.22 24.42	1748 1712	2242
3a	110-113 68.8	$C_{11}H_7N_5O_4$ 273.1	48.35 48.37	2.59 2.52	25.64 25.60	1746 1689	2246
3b	183-186 64.2	$C_{12}H_9N_5O_4$ 287.3	50.17 50.20	3.14 3.12	24.39 24.30	1747 1692	2247
3c	154-157 65.5	$C_{12}H_9N_5O_5$ 303.2	47.52 47.61	2.97 2.90	23.10 22.97	1738 1687	2253
4a	see ref. (**3**)	$C_{10}H_7N_5O_2$ 229.2					
4b	225-227 67.1	$C_{11}H_9N_5O_2.½H_2O$ 252.4	52.38 52.61	3.96 3.69	27.77 27.93	1713	2240
4c	219-221 58.4	$C_{11}H_9N_5O_3$ 259.8	50.96 50.74	3.47 3.31	27.03 26.82	1711	2238
5a	214-217 84.8	$C_{11}H_9N_5O_2$ 243.2	54.32 54.49	3.73 3.58	28.79 28.62	1737 1697	2250
5b	179-181 93.9	$C_{12}H_{11}N_5O_2$ 257.7	56.01 56.55	4.31 4.29	27.23 26.97	1731 1689	2240
5c	198-200 96.2	$C_{12}H_{11}N_5O_3$ 273.5	52.73 52.54	4.06 4.12	25.64 25.50	1731 1683	2243
6a	see ref. (**3**) 91.2[b]	$C_{10}H_5N_5O$ 211.2					
6b	285 (dec.) 98.9	$C_{11}H_7N_5O.½H_2O$ 225.2	56.41 56.83	3.43 3.77	29.91 29.42	1637	2238
6c	306-308 97.5	$C_{11}H_7N_5O_2.H_2O$ 259.3	50.96 51.43	3.47 3.60	27.04 26.74	1666	2239
8a	271-274 82.3[b];62.9[d]; 68[e]	$C_{11}H_7N_5O$ 225.2	58.67 58.79	3.13 2.97	31.10 30.52	1688	2240
8b	260-263 65.2[d];81.3[e]	$C_{12}H_9N_5O$ 239.3	60.23 60.58	3.79 3.76	29.29 29.33	1687	2243
8c	270-273 61.6[d];76.7[e]	$C_{12}H_9N_5O_2$ 254.5	56.45 56.35	3.56 3.60	27.45 27.21	1691	2236

[a] reflux in xylene, [b] reflux in anisole [c] cyclization in basic solution [d] reflux in acetic acid [e] methylation with CH_3I

Table 2
^{1}H-NMR spectra of compounds 1-8

Compound	^{1}H-NMR spectrum
1a	1.33(t, 3H, J=7.0, CH_3); 4.26(q, 2H, J=7.0, CH_2); 7.40(t, 1H, J=7.7, H_4); 7.90(t, 1H, J=7.7, H_5); 8.24(d, 1H, J=7.5, H_6); 8.54(d, 1H, J=7.5, H_5); 11.17(s, 1H, NH); 11.91(s, 1H, NH)
1b	1.33(t, 3H, J=7.1, CH_3); 2.45(s, 3H, CH_3); 4.26(q, 2H, J=7.1, CH_2); 7.74(d, 1H, J=8.4, H_5); 8.07(s, 1H, H_3); 8.46(d, 1H, J=8.4, H_6); 11.14(s, 1H, NH); 11.81(s, 1H, NH)
1c	1.32(t, 3H, J=7.1, CH_3); 3.93(s, 3H, OCH_3); 4.25(q, 2H, J=7.1, CH_2); 7.54(d, 1H, J=8.1, H_5); 7.69(s, 1H, H_3); 8.49(d, 1H, J=8.1, H_6); 11.09(s, 1H, NH); 11.78(s, 1H, NH)
2a	7.77(d, 1H, J=8.0, H_6); 7.87(t, 1H, J=7.6, H_4); 8.03(t, 1H, J=7.6, H_5); 8.28(d, 1H, J=8.1, H_3); 13.40(br, 1H, NH)
2b	2.53(s, 3H, CH_3); 7.64(d, 1H, J=8.1, H_6); 7.83 (dd, 1H, J=8.1, J=1.2, H_5); 8.11(d, 1H, J=1.2, H_3); 13.46(br, 1H, NH)
2c	3.98(s, 3H, OCH_3); 7.56(dd, 1H, J=8.9, J=2.9, H_5); 7.68 (d, 1H, J=8.9, H_6); 7.77(d, 1H, J=2.9, H_3); 13.48(br, 1H, NH)
3a	3.29(s, 3H, CH_3); 7.77(dd, 1H, J=7.9, J=1.3, H_6); 7.89(dt, 1H, J=7.7, J=1.4, H_4); 8.05(dt, 1H, J=7.7, J=1.5, H_5); 8.30(dd, 1H, J=8.2, J=1.4, H_3)
3b	2.54(s, 3H, CH_3); 3.28(s, 3H, CH_3); 7.64(d, 1H, J=8.1, H_6); 7.84(dd, 1H, J=8.1, J=1.5, H_5); 8.14(d, 1H, J=1.5, H_3)
3c	3.28(s, 3H, CH_3); 3.99(s, 3H, OCH_3); 7.58(dd, 1H, J=8.7, J=2.9, H_5); 7.68(d, 1H, J=8.7, H_6); 7.80(d, 1H, J=2.9, H_3)
4a	5.52(s, 2H, NH_2); 6.60(t, 1H, J=7.5, H_5); 6.78(d, 1H, J=8.1, H_3); 7.13(d, 1H, J=7.9, H_6); 7.19(t, 1H, J=7.6, H_4); 12.90(br, 1H, NH)
4b	2.25(s, 3H, CH_3); 5.43(s, 2H, NH_2); 6.42(dd, 1H, J=8.0, J=1.0, H_5); 6.58(d, 1H, J=1.0, H_3); 6.99(d, 1H, J=8.0, H_6); 12.90(br, 1H, NH)
4c	3.75(s, 3H, OCH_3); 5.52(s, 2H, NH_2); 6.20(dd, 1H, J=8.7, J=2.7, H_5); 6.31(d, 1H, J=2.7, H_3); 7.02(d, 1H, J=8.7, H_6); 12.88(br, 1H, NH)
5a	3.27(s, 3H, CH_3); 5.54(s, 2H, NH_2); 6.63(dt, 1H, J=7.3, J=0.9, H_5); 6.80(dd, 1H, J=8.1, J=1.0, H_3); 7.12(dd, 1H, J=7.9, J=1.4, H_6); 7.21(dt, 1H, J=7.6, J=1.5, H_4)
5b	2.25(s, 3H, CH_3); 3.26(s, 3H, CH_3); 5.44(s, 2H, NH_2); 6.44(d, 1H, J=8.0, H_5); 6.60(s, 1H, H_3); 6.99(d, 1H, J=8.0, H_6)
5c	3.26(s, 3H, CH_3); 3.75(s, 3H, OCH_3); 5.53(s, 2H, NH_2); 6.22(dd, 1H, J=8.7, J=2.7, H_6); 6.32(d, 1H, J=2.7, H_3); 7.03(d, 1H, J=8.7, H_5)
6a	7.45(t, 1H, J=7.3,H_8); 7.50-7.60(m, 2H, $H_{6,7}$); 7.91(d, 1H, J=7.9, H_9)
6b	2.50(s, 3H, CH_3); 7.27(dd, 1H, J=8.2, J=0.8, H_8); 7.36(d, 1H, J=0.8, H_6); 7.78(d, 1H, J=8.2, H_9)
6c	3.90(s, 3H, OCH_3); 7.00-7.05(m, 2H, $H_{6,8}$); 7.81(dd, 1H, J=8.7, J=0.5, H_9)
8a	3.62(s, 3H, CH_3); 7.46(dt, 1H, J=7.5, J=1.1, H_7); 7.53(dt, 1H, J=7.4, J=1.2, H_8); 7.77(d, 1H, J=7.9, H_6); 7.93(d, 1H, J=7.9, H_9)
8b	2.51(s, 3H, CH_3); 3.61(s, 3H, CH_3); 7.28(dd, 1H, J=8.2, J=0.9, H_8); 7.57(d, 1H, J=0.9, H_6); 7.80(d, 1H, J=8.2, H_9)
8c	3.61(s, 3H, CH_3); 3.89(s, 3H, OCH_3); 7.04(dd, 1H, J=8.8, J=2.3, H_8); 7.33(d, 1H, J=2.3, H_6); 7.83(d, 1H, J=8.8, H_9)