

Cyclization Reactions of Hydrazones XXVI[#]: Synthesis of 2-Aryl-2,3-dihydro-naphto[1',2':4,5]furo[2,3-e]1,2,4-triazin-3-ones and their use for the preparation of 1-Aryl-5-(2-hydroxy-1-naphthyl)-6-azauracils

Jakub Stýskala*, Jan Slouka

Department of Organic Chemistry, Palacky University, Tr. Svobody 8, 771 46 Olomouc, Czech Republic
E-mail: styskala@risc.upol.cz

Abstract: By coupling of diazonium salts with ethyl N-(2-naphto[2,1-b]furyl)-carbamate **5** the corresponding 3-arylazocompounds **6** were obtained, which are tautomeric with their hydrazono form **7**. These ones were thermally cyclized to the corresponding 2-aryl-2,3-dihydro-naphto[1',2':4,5]furo[2,3-e]1,2,4-triazin-3-ones **8**. Compounds **8** were transformed by hydrolytic splitting to the corresponding 1-aryl-5-(2-hydroxy-1-naphthyl)-6-azauracils **9**. Starting carbamate **5** was prepared by a multistep synthesis from 2-hydroxy-1-naphtaldehyde.

Introduction

Within the framework of systematic studies of cyclization reactions of substituted hydrazono-carbamates, we describe herein the synthesis of naphto[2,3-b]furan derivatives and their transformation into naphto[1',2':4,5]furo[2,3-e]1,2,4-triazine derivatives, which has not been described till this time.

Results

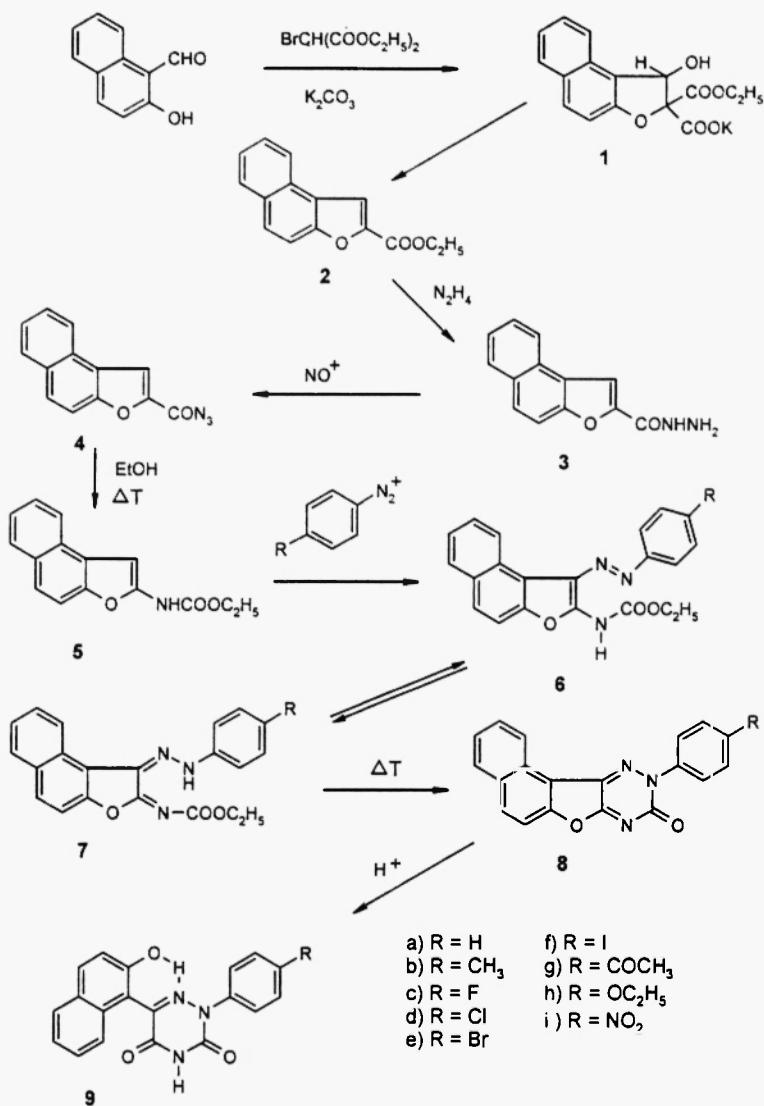
By a coupling reaction of diazonium salts with ethyl N-(2-naphto[2,1-b]furyl)-carbamate **5** in pyridine the corresponding 3-arylazocompounds **6a-6i**, which are tautomeric with hydrazones **7a-7i**, were prepared in good yields. On the basis of some results obtained with analogous benzo[b]furan derivatives (1), we assume, that the corresponding hydrazono-tautomers **7a-7i** are formed also as stable ones.

As a matter of fact boiling the hydrazono carbamates **7** in decalin led to 2-aryl-2,3-dihydro-naphto[1',2':4,5]furo[2,3-e]1,2,4-triazin-3-ones **8**, which represent a novel type of heterocyclic system.

Boiling of compounds **8** in ethanol-water mixture with acid catalysis led to the hydrolytic splitting of furane ring and the formation of the corresponding 1-aryl-5-(2-hydroxy-1-naphthyl)-6-azauracils **9a-9i**.

The starting compound for the preparation of carbamate **5** was ethyl naphto[2,1-b]furan-2-carboxylate **2**, which we prepared by a modified procedure according to Duro at all (2,3) by reaction of diethyl bromomalonate with 2-hydroxy-1-naphtaldehyde in the presence of potassium carbonate. The isolation of potassium 2-ethoxycarbonyl-3-hydroxy-2,3-dihydro-naphto[2,1-b]furan-2-carboxylate **1** could be achieved, as an intermediate of this reaction. It confirms that the reaction is started by aldolisation and nucleophilic substitution with formation of a dihydrofuran ring and followed by the elimination of potassium hydrogen carbonate with formation of compound **2**. The ester **2** was converted by hydrazinolysis to the corresponding hydrazide **3**. For the transformation of hydrazide **3** to the azide **4** we successfully used nitrosation in perchloric acid solution as the most efficient method. The azide **4** was converted to carbamate **5** by boiling in anhydrous ethanol for a prolonged period of time.

[#]Part XXV: see ref. (5)



1. Reaction scheme

Apparatus and methods

The melting points were determined on a Boetius stage and are uncorrected. The infrared spectra were recorded in KBr wafers and scanned on an ATI Unicam Genesis FTIR instrument. The NMR spectra were registered in (CD₃)₂SO on a Bruker AMX-360 spectrometer (360 MHz); the chemical shifts are reported in ppm. Elemental analyses were performed with an EA 1108 Elemental Analyser (Fison Instrument).

Experimental

Potassium 2-ethoxycarbonyl-3-hydroxy-2,3-dihydro-naphto[2,1-b]furan-2-carboxylate 1

A mixture of 2-hydroxy-1-naphthaldehyde (21.5 g, 125 mmol), diethyl bromomalonate (30.4 g, 127 mmol), anhydrous potassium carbonate (30.18 g, 218 mmol) in anhydrous ethanol (100 ml) was refluxed for 4 h. The undissolved solid (ca. 50 g) was filtered off, washed four times with ethanol (50 ml portions), suspended twice in cold water (80 ml), collected on a filter and dried to yield 1 (14.9 g, 35 %), mp above 300 °C.

¹H-NMR: 1.19 (3H,t,CH₃); 4.05-6.16 (2H,m,CH₂ as a prochiral group); 5.75 (1H,s,H); 7.27 (1H,d,arom.); 7.36 (1H,t,arom.); 7.53 (1H,t,arom.); 7.85 (1H,d,arom.); 7.90 (2H,t,arom.); 8.68 (1H,brs,OH). IR (cm⁻¹): 1743, 1626, 1363, 1212, 1027. C₁₆H₁₃KO₃ (340.4) calcd C 56.46, H 3.85; found C 56.1, H 4.1

Ethyl naphto[2,1-b]furan-2-carboxylate 2

a) The ethanolic extract from the previous procedure was evaporated to dryness. The deeply dark residue was dissolved in hot a ethanol-water mixture (3:1), treated with charcoal and left to stand overnight in a cold place. The precipitated crystalline compound was filtered off and dried to yield 2 (13.5 g, 45 %), mp 96-98°C (ref. (3) mp 97-98°C).

b) A mixture of salt 1 (1.0 g, 2.94 mmol) and water (4 ml) was refluxed for 2 minutes. The formed emulsion was allowed to stand in cold place to give crystalline compound. The compound was collected by suction, washed with water and dried to yield 2 (0.63 g, 89 %). ¹H-NMR: 1.39 (3H,t,CH₃); 4.41 (2H,q,CH₂); 7.61 (1H,t,arom.); 7.70 (1H,t,arom.); 7.87 (1H,d,arom.); 8.03 (1H,d,arom.); 8.08 (1H,d,arom.); 8.43 (1H,s,arom.); 8.45 (1H,d,arom.). IR (cm⁻¹): 2987, 1728, 1553, 1327, 1173. C₁₅H₁₂O₃ (240.2) calcd C 74.99, C 5.03; found C 47.8, H 5.1

Naphto[2,1-b]furan-2-carbonylhydrazide 3

Hydrazine hydrate (80%, 18.0 ml, 460 mmol) was added to the solution of ester 2 (30.0 g, 125 mmol) in hot anhydrous ethanol (60 ml) and the reaction mixture was refluxed for 90 minutes. Upon cooling, the precipitated colourless crystalline hydrazide was collected on filter, washed three times with ethanol (30 ml portions) and dried in air to yield 3 (26.3 g, 93 %), mp 245-250 °C, which is in agreement with ref. (4). ¹H-NMR: 4.60 (2H,s,NH); 7.58 (1H,t,arom.); 7.68 (1H,t,arom.); 7.81 (1H,d,arom.); 7.97 (1H,d,arom.); 8.07 (1H,d,arom.); 8.17 (1H,d,arom.); 8.33 (1H,d,arom.); 10.01 (1H,brs,NH). IR (cm⁻¹): 3474, 3304, 1658, 1596, 1328, 1189. C₁₃H₁₀N₂O₂ (226.2) calcd C 69.02, H 4.46, N 12.38; found C 69.1, H 4.2, N 12.3

Naphto[2,1-b]furan-2-carbonylazide 4

A solution of perchloric acid (70%, ca. 40 ml) was added to the suspension of hydrazide 3 (10.0 g, 44.2 mmol) in boiling water (1000 ml) to give a clear solution. The solution was well-stirred and cooled to 2 °C. A solution of sodium nitrite (3.05 g, 44.2 mmol) in ice water (30 ml) was added to the resulting microcrystalline suspension portionwise with stirring over a period of about 1 h. The reaction mixture was stirred for next 3 h at 0-4°C and allowed to stand overnight in a refrigerator. The next day, azide 4 was collected on filter, washed with water and dried over phosphorus pentoxide *in vacuo* in the dark to avoid partial decomposition. The yield 10.4 g (99 %), mp 132-134 °C dec. ¹H-NMR: 7.66 (1H,t,arom.); 7.76 (1H,t,arom.); 7.94 (1H,d,arom.); 8.14 (2H,d,arom.); 8.53 (1H,d,arom.); 8.64 (1H,s,arom.). IR (cm⁻¹): 2205, 2146, 1692, 1542, 1328, 1182, 1021. C₁₃H₇N₃O₂ (237.2) calcd C 65.82, H 2.97, N 17.71; found C 65.9, H 2.7, N 17.5

Ethyl N-(2-naphto[2,1-b]furyl)-carbamate 5

A mixture of azide 4 (5.2 g, 21.9 mmol) and anhydrous ethanol (100 ml) was refluxed for 3.5 h to give a solution, which was filtered with charcoal. The filtrate was diluted with warm water to yield a gentle turbidity and cooled. The next day, crystalline compound was filtered off and washed with ethanol-water mixture (1:1) to yield 5 (3.73 g, 66 %), mp 120-122 °C. ¹H-NMR: 1.33 (3H,t,CH₃); 4.26 (2H,q,CH₂); 7.09 (1H,s,arom.); 7.53 (1H,t,arom.); 7.61 (1H,t,arom.); 7.73 (2H,m,arom.); 8.03 (1H,d,arom.); 8.25 (1H,d,arom.); 10.89 (1H,brs,NH). IR (cm⁻¹): 3397, 2983, 1740, 1609, 1530, 1269, 1203. C₁₅H₁₃NO₃ (255.3) calcd C 70.58, H 5.13, N 5.49; found C 70.5, H 5.2, N 5.2

Ethyl N-(3-arylhydrazono-2,3-dihydro-naphto[2,1-b]furan-2-ylidene)-carbamates 7a-7i

General procedure

A solution of the corresponding aromatic amine (1.00 mmol) in a mixture of ice water (5 ml) and hydrochloric acid (37%, 0.6 ml) was diazotized by sodium nitrite (69 mg, 1.00 mmol) in ice water (4 ml). The

mixture was stirred in ice bath for 15 min. and then added portionwise to the solution of urethane **5** (255 mg, 1.00 mmol) in pyridine (20 ml), which was cooled to 0 – 5 °C. The mixture was left to stand at 0 – 5 °C for 24 h and then slowly diluted with ice water to a total volume 500 ml. The next day the precipitated dark orange solid was collected by suction, washed with water and dried. The sample for analysis was obtained by the recrystallisation from an ethanol-benzene mixture. The purity of these compounds was controlled by TLC on silicagel plate using benzene as the mobile phase. For further details, see tables 1 and 4.

2-Aryl-2,3-dihydro-naphto[1'2'4,5]furo[2,3-e]1,2,4-triazin-3-ones **8a-8i**

General procedure

A solution of the corresponding hydrazonocarbamate **7** (0.6 mmol) in boiling decalin (4 ml) was refluxed for 1 h and then cooled. After several hours the yellow solid was collected by suction, washed with hexane and dried at 110 °C *in vacuo*. The sample for analysis was obtained by the recrystallisation from benzene. The purity of these compounds was controlled by TLC on silicagel plate using a chloroform-methanol (40:1) mixture as the mobile phase. For further details, see tables 2 and 4.

2-Aryl-6-(2-hydroxy-1-naphthyl)-2,3,4,5-tetrahydro-1,2,4-triazin-3,5-diones **9a-9i**

General procedure

A solution of the corresponding compound **8** (0.2 mmol) in hydrochloric acid (37%, 0.5 ml) and ethanol (10 ml) was refluxed for 15 min. and then evaporated to dryness. The residue was dried at 120 °C and then recrystallised from a ethanol-water mixture (1:1). The sample for analysis was dried at 120 °C for 2 h to remove one molecule of crystal water which is always present in these compounds. The purity of these compounds was controlled by TLC on silicagel plate using a chloroform-methanol (40:2) mixture as the mobile phase. For further details, see tables 3 and 4.

Table 1

Characteristic data of compounds **7**

Compound	M.p. (°C) Yield (%)	Formula M.w.	Elemental analysis (Calculated/Found)			$\nu(C=O)$ cm^{-1}
			% C	% H	% N	
7a	155-157 73	$C_{21}H_{17}N_3O_3$ 359.4	70.18 69.8	4.77 4.8	11.69 11.3	1733, 1680
7b	151-153 84	$C_{22}H_{19}N_3O_3$ 373.4	70.76 70.7	5.13 5.2	11.25 11.2	1730, 1686
7c	157-160 35	$C_{21}H_{16}N_3O_3F$ 377.4	66.84 66.8	4.27 4.2	11.13 10.9	1715, 1667
7d	147-150 84	$C_{21}H_{16}N_3O_3Cl$ 393.8	64.11 64.2	4.10 4.0	10.69 10.3	1734, 1676
7e	166-168 84	$C_{21}H_{16}N_3O_3Br$ 438.3	57.55 57.6	3.68 3.6	9.59 9.4	1733, 1676
7f	172-175 82	$C_{21}H_{16}N_3O_3I$ 485.3	51.98 52.2	3.32 3.1	8.66 8.4	1720, 1673
7g	182-184 81	$C_{23}H_{19}N_3O_4$ 401.4	68.82 69.1	4.77 4.6	10.47 10.4	1725, 1676
7h	146-148 77	$C_{23}H_{21}N_3O_4$ 403.4	68.47 68.6	5.25 5.0	10.42 10.0	1721, 1669
7i	231-234 86	$C_{21}H_{16}N_4O_5$ 404.4	62.37 62.5	3.99 3.9	13.85 13.7	1733, 1684

Table 2
Characteristic data of compounds 8

Compound	M.p. (°C) Yield (%)	Formula M.w.	Elemental analysis (Calculated/Found)			$\nu(\text{C=O})$ cm^{-1}
			% C	% H	% N	
8a	287-290 87	$\text{C}_{19}\text{H}_{11}\text{N}_3\text{O}_2$ 313.3	72.84 72.8	3.54 3.8	13.41 13.2	1676, 1661
8b	282-284 91	$\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_2$ 327.3	73.38 73.7	4.00 4.3	12.84 12.6	1692, 1672
8c	275-277 60	$\text{C}_{19}\text{H}_{10}\text{N}_3\text{O}_2\text{F}$ 331.3	68.88 68.7	3.04 3.3	12.68 12.5	1692, 1662
8d	305-307 78	$\text{C}_{19}\text{H}_{10}\text{N}_3\text{O}_2\text{Cl}$ 347.7	65.62 65.4	2.90 3.2	12.08 12.0	1690, 1667
8e	310-312 87	$\text{C}_{19}\text{H}_{10}\text{N}_3\text{O}_2\text{Br}$ 392.2	58.19 58.0	2.57 2.7	10.71 10.5	1687, 1667
8f	315-317 84	$\text{C}_{19}\text{H}_{10}\text{N}_3\text{O}_2\text{I}$ 439.2	51.96 52.2	2.29 2.4	9.57 9.4	1686, 1668
8g	287-290 90	$\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_3$ 355.3	70.98 71.2	3.69 3.8	11.82 11.6	1697, 1676, 1668
8h	284-287 87	$\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_3$ 357.3	70.58 70.8	4.23 4.0	11.76 11.5	1697, 1667
8i	354-355 89	$\text{C}_{19}\text{H}_{10}\text{N}_4\text{O}_4$ 358.3	63.69 63.4	2.81 3.1	15.64 15.4	1694, 1670

Table 3
Characteristic data of compounds 9

Compound	M.p. (°C) Yield (%)	Formula M.w.	Elemental analysis (Calculated/Found)			$\nu(\text{C=O})$ cm^{-1}
			% C	% H	% N	
9a	236-239 96	$\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_3$ 331.3	68.88 69.0	3.95 3.9	12.68 12.6	1704, 1683
9b	253-256 98	$\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_3$ 345.4	69.56 69.5	4.38 4.3	12.17 12.0	1713, 1693
9c	227-230 95	$\text{C}_{19}\text{H}_{12}\text{N}_3\text{O}_3\text{F}$ 349.3	65.33 65.3	3.46 3.4	12.03 11.9	1725, 1692
9d	286-289 96	$\text{C}_{19}\text{H}_{12}\text{N}_3\text{O}_3\text{Cl}$ 365.8	62.39 62.3	3.31 3.2	11.49 11.3	1727, 1690
9e	297-300 98	$\text{C}_{19}\text{H}_{12}\text{N}_3\text{O}_3\text{Br}$ 410.2	55.63 55.7	2.95 3.0	10.24 10.1	1727, 1690
9f	292-295 97	$\text{C}_{19}\text{H}_{12}\text{N}_3\text{O}_3\text{I}$ 457.2	49.91 50.0	2.65 2.6	9.19 9.0	1728, 1688
9g	283-286 98	$\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_4$ 373.4	67.56 67.7	4.05 4.1	11.25 11.1	1726, 1701, 1656
9h	211-213 98	$\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_4$ 375.4	67.19 67.8	4.56 4.7	11.19 11.0	1706, 1680
9i	289-292 97	$\text{C}_{19}\text{H}_{12}\text{N}_4\text{O}_5$ 376.3	60.64 60.7	3.21 3.3	14.89 14.6	1730, 1692

Table 4¹H-NMR spectra of some compounds 7,8,9

Compound	¹ H-NMR spectrum
7a	1.39 (3H,t,CH ₃); 4.37 (2H,q,CH ₂); 7.20 (1H,t,arom.); 7.52 (2H,t,arom.); 7.62-7.64 (4H,m,arom.); 7.81 (1H,t,arom.); 8.05 (1H,d,arom.); 8.09 (1H,d,arom.); 8.83 (1H,d,arom.); 12.30 (1H,brs,NH)
7d	1.39 (3H,t,CH ₃); 4.37 (2H,q,CH ₂); 7.50-7.64 (6H,m,arom.); 7.76 (1H,t,arom.); 8.01 (1H,d,arom.); 8.05 (1H,d,arom.); 8.71 (1H,d,arom.); 12.22 (1H,brs,NH)
7h	1.37 (3H,t,CH ₃); 1.39 (3H,t,CH ₃); 4.11 (2H,q,CH ₂); 4.34 (2H,q,CH ₂); 7.10 (2H,d,arom.); 7.61-7.67 (4H,m,arom.); 7.78 (1H,t,arom.); 8.00 (1H,d,arom.); 8.09 (1H,d,arom.); 8.85 (1H,d,arom.); 12.13 (1H,brs,NH)
8a	7.57 (1H,t,arom.); 7.66 (2H,t,arom.); 7.72 (1H,t,arom.); 7.76 (2H,d,arom.); 7.84 (1H,t,arom.); 8.00 (1H,d,arom.); 8.24 (1H,d,arom.); 8.39 (1H,d,arom.); 8.45 (1H,d,arom.)
8d	7.70-7.75 (3H,m,arom.); 7.80-7.84 (2H,m,arom.); 7.87 (1H,t,arom.); 8.01 (1H,d,arom.); 8.24 (1H,d,arom.); 8.41 (1H,d,arom.); 8.45 (1H,d,arom.)
8h	1.43 (3H,t,CH ₃); 4.12 (2H,q,CH ₂); 7.17 (2H,d,arom.); 7.67 (2H,d,arom.); 7.72 (1H,t,arom.); 7.68 (1H,t,arom.); 8.00 (1H,d,arom.); 8.24 (1H,d,arom.); 8.38 (1H,d,arom.); 8.46 (1H,d,arom.)
9a	7.24 (1H,d,arom.); 7.36 (1H,t,arom.); 7.42-7.48 (2H,m,arom.); 7.52 (2H,t,arom.); 7.60 (2H,d,arom.); 7.82 (1H,d,arom.); 7.88 (1H,d,arom.); 7.93 (1H,d,arom.); 9.96 (1H,brs,OH); 12.37 (1H,brs,NH)
9d	7.25 (1H,d,arom.); 7.36 (1H,t,arom.); 7.46 (1H,t,arom.); 7.58-7.67 (4H,m,arom.); 7.86 (1H,d,arom.); 7.87 (1H,d,arom.); 7.94 (1H,d,arom.); 9.59 (1H,brs,OH); 12.55 (1H,brs,NH)
9h	1.37 (3H,t,CH ₃); 4.09 (2H,q,CH ₂); 7.04 (2H,d,arom.); 7.24 (1H,d,arom.); 7.35 (1H,t,arom.); 7.45 (1H,t,arom.); 7.50 (2H,d,arom.); 7.81 (1H,d,arom.); 7.89 (1H,d,arom.); 7.92 (1H,d,arom.); 9.95 (1H,brs,OH); 12.47 (1H,brs,NH)

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