Synthesis of the 4,10-Dihydro-3H-pyridazino[1,6-b]isoquinolin-10-one System by a Furan Recyclization Reaction

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Abstract: The novel 4,10-dihydro-3H-pyridazino[1,6-b]isoquinolin-10-one heterocyclic system was synthesized by acid-catalyzed recyclization of 2-(difurylmethyl)benzohydrazides as well as by recyclization of (2-carboxyaryl)difurylmethanes to isocoumarins followed by the reaction with hydrazine hydrate.

Key words: furans, ring opening, ring closure, fused-ring system, pyridazino[1,6-b]isoquinolinone

Among the huge diversity of chemical properties of furan derivatives,¹ their acid-catalyzed transformation into 1,4-diketones is one of the most important processes. It is widely used in laboratory practice,² because of the ability of the thus-formed diketones to participate in different reactions. In some cases, dicarbonyl compounds are so prone to these transformations that they cannot be isolated from the reaction mixture. There are also examples of furan recyclizations without the intermediacy of a diketone at all. In these reactions, the furan ring can be considered to be a formal equivalent of a 1,4-dicarbonyl compound. Both masked carbonyl groups are usually involved in the formation of new heterocycles during these acid-catalyzed reactions of furan derivatives with nucleophiles.³ A limited number of examples of similar intramolecular transformations have also been described.⁴

Over the past years we have developed a general synthesis of benzannelated heterocycles 2 using the recyclization of benzylfurans 1 with different nucleophilic substituents in the ortho position (Scheme 1).⁵ This approach allowed us to synthesize substituted benzofurans,⁶ indoles,⁷ isocoumarins,⁸ isoquinolones,⁹ and isochromenes.¹⁰ In all cases, recyclization proceeded without formation of 1,4-dicarbonyl compounds; a single masked carbonyl group participated in the new ring formation by interaction with the nucleophile located in the ortho position, the other one was liberated in the side chain as a ketone moiety. For benzylfuran starting materials substituted by R¹ represented by another furan ring, the recyclization is often followed by secondary acid-catalyzed intramolecular cyclization with the formation of tetracyclic derivatives 3 (Scheme 1).⁶b,⁷b,⁸a,¹⁰

As a continuation of our studies in this area, we reasoned that the introduction of an additional nucleophile into the benzylfuran molecule may alter the direction of the secondary cyclization and can therefore be applied to the synthesis of new polycyclic heterocycles. We thus showed in a preliminary communication that recyclization of (difurylmethyl)benzohydrazides leads to the formation of 4,10-dihydro-3H-pyridazino[1,6-b]isoquinolin-10-one systems, but not to tetracyclic N-aminoisoquinolone derivatives (Scheme 2).¹¹ Here we describe the full details of this investigation.

As the starting compounds for the synthesis of the corresponding acid hydrazides, we used the readily available

Scheme 1 Benzannelated heterocycles from ortho-substituted benzylfurans

Scheme 2 Formation of annulated tricycles from ortho-substituted benzylfurans
(2-carboxyaryl)difurylmethanes 4a–g (Scheme 3). These acids were converted into the corresponding methyl esters 5a–g in good yields (Scheme 3, Table 1) by treatment with methyl iodide in the presence of a potassium hydroxide dispersion in dimethyl sulfoxide. Reactions of esters 5a–g with hydrazine hydrate in butan-1-ol under reflux yielded hydrazides 6a–g (Scheme 3, Table 1).

Recyclization of hydrazides 6a–g was performed by treatment with a benzene solution of p-toluenesulfonic acid under reflux (Scheme 3). The first step of this recyclization process was the formation of ketones 7a–g, bearing a free amino group. As we expected, the presence of the amino group, which is more nucleophilic than the furan ring, changed the direction of the second cyclization. In this case, heterocyclization occurred rather than the cyclization onto the furan ring, and the sole isolated products were pyridazino[1,6-b]isoquinoline derivatives 8a–g (Scheme 3, Method A). Tetracyclic derivatives 9a–g were not detected in the reaction mixture.

![Scheme 3](image)

**Table 1** Yields of Compounds 5, 6, 8, and 9

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%) of 5</th>
<th>Yield (%) of 6</th>
<th>Yield (%) of 8 from 6</th>
<th>Yield (%) of 8 from 10</th>
<th>Yield (%) of 9</th>
</tr>
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<tr>
<td>a</td>
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<tr>
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<tr>
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<tr>
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<td>87</td>
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Unfortunately, this reaction proceeded with the formation of unidentified byproducts, which were difficult to separate from the target compounds, even by column chromatography. Therefore, we developed an alternative approach to the synthesis of pyridazino[1,6-b]isooquinolines 8a–g (Scheme 3, Method B). This method is based on the relatively facile substitution of an endocyclic isochromone oxygen atom by nitrogen-containing nucleophiles such as primary amines, hydroxylamines, or hydrazines. For this approach we used the same acids 4a–g as starting compounds (Scheme 3). These acids were transformed into ketones 10a–g by a reaction sequence earlier developed by us. Ketones 10a–g reacted with hydrazine hydrate in ethylene glycol at room temperature to give the corresponding hydrazones 11a–g. Subsequent reflux of the resulting solutions for 15 minutes readily yielded the target pyridazino[1,6-b]isooquinolines 8a–g (Scheme 3). It should be noted that method B is simpler from a preparative point of view and gives higher overall yields based on the starting compounds 4. Nevertheless, tetracyclic N-aminoisooquinolones 9 cannot be synthesized by recyclization of hydrazides 6, but some of these compounds were prepared in good yields by reflux of isochromones 12 with hydrazine hydrate in ethylene glycol (Scheme 3). We have also demonstrated that 4,10-dihydro-3H-pyridazino[1,6-b]isooquinolin-10-ones 8 can be readily dehydrogenated by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Scheme 4).

Melting points are uncorrected. 1H and 13C NMR spectra of samples in CDCl3 and DMSO-d6 were recorded on Bruker AC 200, Bruker WM 250, Bruker DPX 300, and Bruker AVANCE 600 spectrometers. Chemical shifts are reported in ppm relative to TMS as an internal standard. Mass spectra were recorded on a Kratos MS-30 instrument with 70-eV EI ionization at 200 °C. IR spectra of samples prepared as KBr plates were measured on InfraLUM FT-02 and InfraLUM FT-801 instruments. Column chromatography was carried out on silica gel KSK (5–40 μm) manufactured by LTD Sorbopolymer.

Compounds 5a–g; General Procedure
To a suspension of finely powdered KOH (2 g) in anhyd DMSO (40 mL) were added the appropriate compound 4 (6.76 mmol) and Mel (2 mL, 12.12 mmol), and the mixture was stirred at r.t. for 20 min. The suspension was removed by filtration, and the filtrate was poured into H2O (500 mL). The resulting emulsion was brought to pH 5–6 with dilute HCl and extracted with CH2Cl2 (4 × 30 mL). The combined extract was dried (Na2SO4) and evaporated to dryness. The residue was purified by flash column chromatography (silica gel, hexane–CH2Cl2, 10:1). The eluate containing the target compound was reduced in volume to 10–20 mL and left to crystallize at <0 °C.

Methyl 2-[Bis(5-methyl-2-furyl)methyl]benzoate (5a)
Yield: 1.80 g (86%); white solid; mp 62–63 °C.

IR (KBr): 3434, 2950, 2919, 1727, 1609, 1555, 1434, 1285, 1238, 1141, 1076, 1021, 970, 767 cm–1.

Compounds 13 Prepared by Dehydrogenation of Dihydopyridazinoisooquinolones 8

In conclusion, we have developed two alternative syntheses of the novel heterocyclic system 4,10-dihydro-3H-pyridazino[1,6-b]isooquinolin-10-one. This system incorporates pyridazine and isooquinoline pharmacophores. Both of them are present in many drugs with different modes of action. Therefore, the synthesized pyridazino[1,6-b]isooquinolines may be of interest for biological screening. Our approach to the preparation of these compounds has extended the scope of ortho-substituted benzyluran recyclizations yielding a broad range of benzannelated heterocycles. We believe that the proposed sequence of recyclization–nucleophile-directed cyclization can also be applied to the synthesis of other tricyclic heterocycles.

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3-HAr), 6.47 (s, 1 H, CH), 7.17 (d, J = 8.5 Hz, 1 H, HAr), 7.56 (dd, J = 2.3, 8.5 Hz, 1 H, HAr), 8.05 (d, J = 2.3 Hz, 1 H, HAr).


**Methyl 2-[Bis(5-methyl-2-furyl)methyl]-5-iodobenzoate (5d)**

Yield: 2.50 g (85%); white solid; mp 99–100 °C.

**Methyl 2-[Bis(5-methyl-2-furyl)methyl]-4-chlorobenzoate (5e)**

Yield: 2.16 g (82%); white solid; mp 81–82 °C.

**Methyl 2-[Bis(5-methyl-2-furyl)methyl]-4-bromobenzoate (5f)**

Yield: 1.98 g (85%); white solid; mp 75–76 °C.

**Methyl 2-[Bis(5-methyl-2-furyl)methyl]-3-chlorobenzoate (5g)**

Yield: 1.78 g (82%); white solid; mp 103–104 °C.

**Synthesis of the 4,10-Dihydro-3H-pyridazino[1,6-b]isoquinolin-10-one System**

Yield: 489 mg (40%, Method A), 581 mg (59%, Method B); yellow solid; mp 183–184 °C.

IR (KBr): 3432, 2952, 2920, 1718, 1655, 1553, 1480, 1438, 1391, 1360, 1348, 1285, 1262, 1234, 1105, 1075, 1021, 974, 911, 841, 784, 755 cm⁻¹.

**Compounds 6a–g; General Procedure**

A mixture of the appropriate compound of 4 (5.81 mmol), NH₂NH₂·H₂O (9 mL) and n-BuOH (9 mL) was refluxed for 20 min. Then it was poured into H₂O (300 mL). The resulting precipitate was collected by filtration, air-dried, and used in the next step without further purification.

**Compounds 8a–g; General Procedure**

**Method A**

To a 15% soln of TsOH in benzene (20 mL) prepared by refluxing TsOH·H₂O in benzene with azeotropic removal of H₂O, compound 6 (4.19 mmol) was added and the mixture was refluxed for 10 min. The resulting soln was poured into H₂O (300 mL). The slurry was extracted with CHCl₃ (3 × 50 mL). The combined extract was washed with H₂O, dried (Na₂SO₄), and evaporated to dryness. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1). The solvent was removed and the residue was recrystallized (hexane–EtOAc, 10:1) at <0 °C.

**Method B**

A suspension of compound 10 (3.37 mmol) in ethylene glycol (50 mL) with NH₂NH₂·H₂O (1 mL) was stirred at r.t. until complete dissolution of the starting material (30 min, TLC monitoring). The resulting soln was refluxed for 15 min, poured into H₂O (300 mL) and extracted with CHCl₃ (3 × 50 mL). The combined extract was washed with H₂O, dried (Na₂SO₄), and evaporated to dryness. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1). The solvent was removed and the residue was recrystallized (hexane–EtOAc, 10:1) at <0 °C.

**2-Methyl-5-(5-methyl-2-furyl)-3,4-dihydro-10H-pyridazino[1,6-b]isoquinolin-10-one (8a)**

Yield: 489 mg (40%, Method A), 581 mg (59%, Method B); yellow solid; mp 183–184 °C.

**8-Chloro-2-methyl-5-(5-methyl-2-furyl)-3,4-dihydro-10H-pyridazino[1,6-b]isoquinolin-10-one (8b)**

Yield: 739 mg (54%, Method A), 572 mg (52%, Method B); yellow solid; mp 173–174 °C.
MS (EI, 70 eV); m/z (%) = 373/371 (20/20), [M+1]^+, 372/370 (95/100) [M^+], 329 (15), 327 (14), 290 (12), 288 (11).

Anal. Calc'd for C_{18}H_{15}BrN_{2}O_{2}: C, 58.24; H, 4.07. Found: C, 58.27; H, 4.02.

7-Iodo-2-methyl-5-(5-methyl-2-furyl)-3,4-dihydro-10H-pyridazino[1,6-f]isoquinolin-10-one (8g)

Yield: 910 mg (52%, Method A), 718 mg (51%, Method B); yellow solid; mp 201–202 °C.

IR (KBr): 1665, 1591, 1545, 1465, 1346, 1218, 1181, 1153, 1079, 1019, 867, 791 cm⁻¹.

1H NMR (300 MHz, CDCl₃); δ = 2.30–2.35 (m, 2 H, CH₂), 2.33 (s, 3 H, CH₃), 2.37 (s, 3 H, CH₃), 2.81–2.86 (m, 2 H, CH₂), 6.15 (d, J = 3.0 Hz, 1 H, 4-H_py), 6.32 (d, J = 3.0 Hz, 1 H, 3-H_py), 7.36 (d, J = 1.8 Hz, 1 H, H₂ar), 7.32 (d, J = 1.8 Hz, 1 H, H₂ar), 8.47 (d, J = 8.5 Hz, 1 H, H₂ar).

13C NMR (50 MHz, CDCl₃); δ = 27.6, 27.8, 28.1, 103.8, 105.7, 116.1, 122.7, 124.1, 125.5, 126.1, 126.4, 127.4, 131.2, 132.5, 132.8, 136.3, 137.5, 163.6, 163.9.

MS (EI, 70 eV): m/z (%) = 368 (15), 355 (10), 332 (11), 327 (19), 288 (14), 151 (16).

Anal. Calc'd for C_{18}H_{15}BrN_{2}O_{2}: C, 58.24; H, 4.07. Found: C, 58.21; H, 4.02.

Compounds 9a,c,f; General Procedure

A mixture of the appropriate compound 12 (3 mmol), NH₂NH₂·H₂O (2 mL), and ethylene glycol (55 mL) was refluxed for 5–10 min (TLC monitoring). Then it was poured into H₂O (500 mL). The resulting precipitate was collected by filtration, air-dried, and recrystallized (EtOH).

7-Amino-2,4-dimethyl-6,7-dihydro-8H-furo[2',3':3,4]cyclohepta[1,2-c]isoquinolin-8-one (9a)

Yield: 543 mg (62%); pale yellow needles; mp 192–193 °C.

IR (KBr): 3289, 3206, 1620, 1574, 1484, 1344, 984, 826, 767, 686 cm⁻¹.

1H NMR (600 MHz, DMSO-d₆); δ = 1.80–2.70 (br m, 1 H, CH₂), 1.98 (s, 3 H, CH₃), 2.46 (s, 3 H, CH₃), 3.90–4.80 (br m, 1 H, CH₂), 5.43–5.51 (m, 1 H, =CH), 6.02 (s, 2 H, NH₂), 6.50 (s, 1 H, H₂ar), 7.50–7.53 (m, 1 H, H₂ar), 7.73–7.76 (m, 1 H, H₂ar), 8.30–8.31 (m, 1 H, H₂ar), 8.40–8.41 (m, 1 H, H₂ar).

13C NMR (150 MHz, CDCl₃); δ = 13.5, 19.7, 27.8, 103.9, 105.7, 116.2, 122.7, 124.1, 125.9, 126.1, 127.4, 131.2, 132.5, 132.8, 136.3, 147.9, 150.3, 160.1.

MS (EI, 70 eV); m/z (%) = 293/291 (17/17), 292/290 (100/100) [M^+], 277 (44), 276 (100), 275 (21), 263 (10), 262 (59), 247 (36), 149 (19).

Anal. Calc'd for C_{18}H_{15}BrN_{2}O_{2}: C, 73.96; H, 5.52. Found: C, 73.86; H, 5.32.

7-Amino-2,4-dimethyl-6,7-dihydro-8H-furo[2',3';3,4]cyclohepta[1,2-c]isoquinolin-8-one (9c)

Yield: 712 mg (64%); pale yellow needles; mp 250 °C.

IR (KBr): 3291, 3210, 1629, 1576, 1481, 1343, 895, 822, 786 cm⁻¹.

1H NMR (600 MHz, DMSO-d₆); δ = 1.90–2.75 (br m, 1 H, CH₂), 1.99 (s, 3 H, CH₃), 2.47 (s, 3 H, CH₃), 4.00–4.85 (br m, 1 H, CH₂), 5.42–5.45 (m, 1 H, =CH), 6.05 (s, 2 H, NH₂), 6.52 (s, 1 H, H₂ar), 7.77 (dd, J = 2.4, 9.0 Hz, 1 H, H₂ar), 8.22 (d, J = 2.4 Hz, 1 H, H₂ar), 8.42 (d, J = 9.0 Hz, 1 H, H₂ar).

13C NMR (150 MHz, DMSO-d₆); δ = 13.5, 19.7, 27.8, 103.6, 105.8, 116.1, 123.9, 126.1, 126.2, 126.6, 130.6, 131.2, 131.4, 132.5, 136.6, 147.4, 150.5, 159.1.
7-Amino-11-bromo-2,4-dimethyl-6,7-dihydro-8H-furo[2,3,4]cy clohepta[1,2-c]isoquinolin-8-one (9f)
Yield: 690 mg (62%); pale yellow needles; mp 255 °C.
IR (KBr): 3288, 3206, 1627, 1570, 1003, 926, 829, 773 cm⁻¹.

1H NMR (600 MHz, DMSO-d₆): δ = 1.85–2.70 (br m, 1 H, CH2), 1.99 (s, 3 H, CH₃), 2.47 (s, 3 H, CH₃), 3.95–4.80 (br m, 1 H, CH₂), 5.43–5.45 (m, 1 H, CH), 6.02 (s, 1 H, NH₂), 6.54 (s, 1 H, Hₕₗ⁻), 7.68 (dd, J = 1.9, 8.6 Hz, 1 H, Hₕₜ⁻), 8.22 (d, J = 8.6 Hz, 1 H, Hₕₜ⁺), 8.53 (d, J = 1.9 Hz, 1 H, Hₕₜ⁺).

13C NMR (150 MHz, DMSO-d₆): δ = 135.1, 14.7, 27.9, 102.8, 105.9, 116.2, 121.5, 126.0, 126.1, 129.0, 129.8, 131.3, 134.2, 137.7, 147.2, 150.4, 159.7.

MS (EI, 70 eV): m/z (%) = 373/371 (6/6) [M⁺ + 1], 372/370 (21/21) [M⁺], 357 (54), 355 (100), 353 (41), 342 (34), 340 (34), 327 (17), 325 (19), 232 (13).


8-Bromo-2-ethyl-5-(5-methyl-2-furyl)-10H-pyridoizinol-1,6-bisoquinolin-10-one (13c)
Yield: 221 mg (60%); orange needles; mp 236–237 °C.
IR (KBr): 1680, 1516, 1463, 1397, 1203, 876, 822, 791 cm⁻¹.

1H NMR (600 MHz, DMSO-d₆): δ = 2.37 (s, 3 H, CH₃), 2.45 (s, 3 H, CH₃), 3.63 (d, J = 3.0 Hz, 1 H, 4-Hₕₗ⁻), 6.61 (d, J = 3.0 Hz, 1 H, 3-Hₕₗ⁻), 6.98 (d, J = 9.6 Hz, 1 H, Hₕₜ⁻), 7.48 (d, J = 8.4 Hz, 1 H, Hₕₜ⁻), 7.61 (d, J = 9.6 Hz, 1 H, Hₕₜ⁻), 7.95 (dd, J = 2.4, 8.4 Hz, 1 H, Hₕₜ⁻), 8.56 (d, J = 2.4 Hz, 1 H, Hₕₜ⁻).

13C NMR (150 MHz, DMSO-d₆): δ = 135.5, 21.7, 102.2, 107.4, 114.0, 122.3, 123.3, 126.7, 130.0, 130.9, 131.3, 133.1, 137.7, 144.2, 152.9, 153.0, 156.7.

MS (EI, 70 eV): m/z (%) = 371/369 (10/13) [M⁺ + 1], 370/368 (43/48) [M⁺], 328/326 (31/33), 327/325 (100/100), 299 (20), 297 (21), 217 (13), 218 (13), 190 (20), 189 (21), 150 (18).

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