

## Synthesis of masked 2-amino-6-methyl-4-oxo-4H-pyran-3-carbaldehydes

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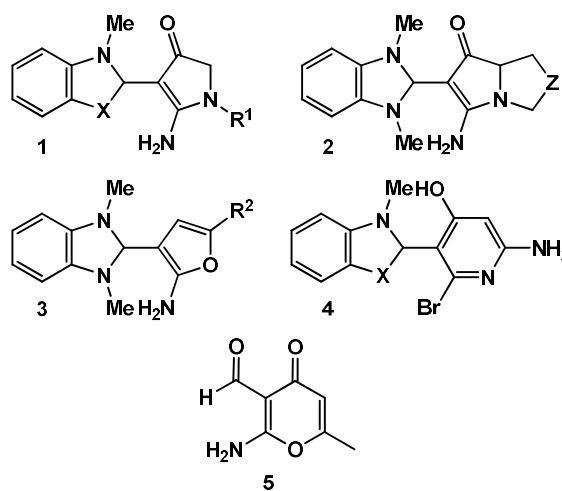
**Keywords:** aminoaldehydes, nitriles, heterocycles, pyranes, hydrazones.

Acetoacetylation of (1,3-dimethylbenzimidazol-2-ylidene)-, (3-methylbenzothiazol-2-ylidene)-, and (3,4-dimethylthiazol-2-ylidene)acetonitriles with 2,2,6-trimethyl-4H-1,3-dioxin-4-one was found to yield appropriate C-acylation products. Treatment of the obtained products with perchloric acid afforded 2-(2-amino-6-methyl-4H-pyran-4-one-3-yl)substituted quaternary azolium salts. Their reduction with sodium borohydride yielded the corresponding dihydro (in the case of benzoazoles) or tetrahydro (in the case of thiazole) derivatives, which were shown to be synthetic equivalents of the title aldehyde.

### Introduction

The *N,N'*-dimethylbenzimidazolium [1–5] and *N*-methylbenzothiazolium [6–9] moieties are well known as synthetic equivalents of aldehyde functionality. Their reduction into 2,3-dihydro derivatives yields the masked formyl group, which can, if necessary, be liberated by hydrolytic cleavage [1–9]. Recently, we successfully employed such an approach for the preparation of masked aldehydes of pyrrole **1** [10], fused pyrrole **2** [11], furan **3** [12] and pyridine **4** [13] series (Figure 1).

In continuation of our research on masked aldehydes we have extended our investigations to the study of 2-amino-6-methyl-4-oxo-4H-pyran-3-carbaldehyde (**5**) derivatives. To the best of our knowledge, such compounds were not described to date.

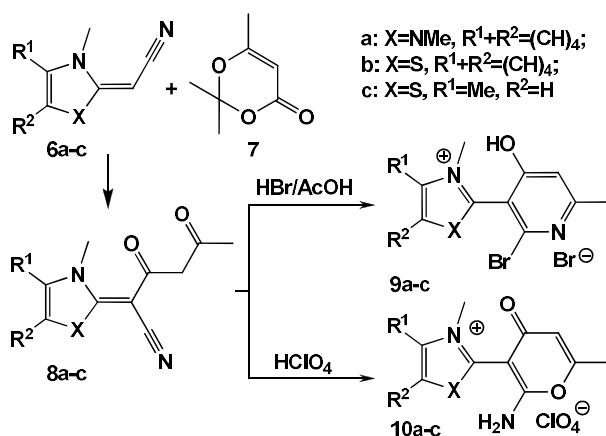


**Figure 1.** Previously prepared masked aldehydes. X = NMe or S; R1 = Alkyl or Ar; R2 = CF<sub>3</sub> or Ar; Z = CH<sub>2</sub> or S.

### Results and Discussion

Treatment of compounds **6a-c** with 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**7**) as widely used agents for acetoacetylation [14–16] was found to yield C-acylation products **8a-c**

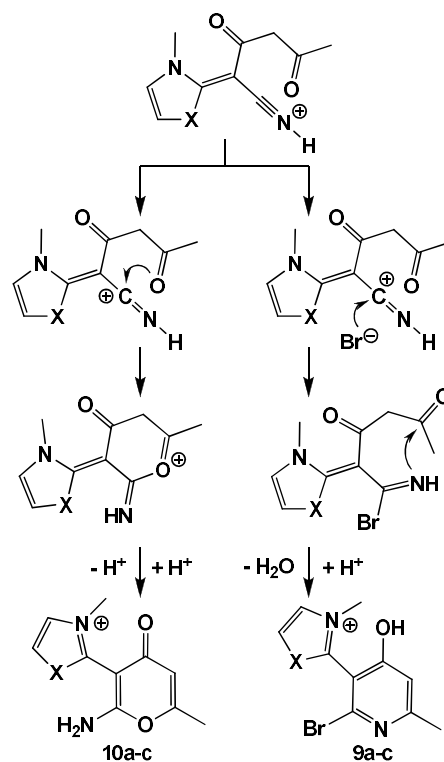
(Scheme 1). It was found that reaction conditions strongly affect cyclization of the compounds **8a-c**. Thus, the use of HBr/AcOH for the cyclization leads to formation of bromopyridines **9a-c**, while the action of perchloric acid gives target aminopyranones **10a-c**.



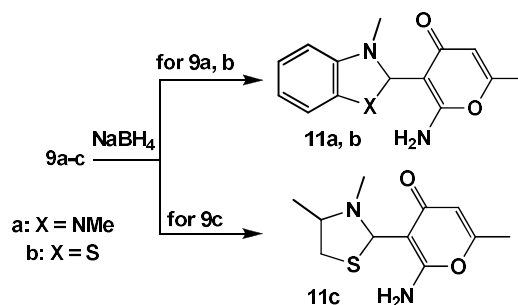
Scheme 1. Synthesis and reactions of derivatives **8a-c**.

Probably the cyclization outcome is defined at the step of cation formation and depends on power of attacking nucleophile (Scheme 2).

Reduction of the quaternary salts **10a** and **10b** with excess sodium borohydride yielded the target masked 2-amino-6-methyl-4-oxo-4*H*-pyran-3-carbaldehyde derivatives **11a** and **11b**, respectively (Scheme 3). In the case of compound **10c**, the reduction resulted in formation of the thiazolidine analogue **11c**, which was similar to the previous results [13]. The structures of the obtained compounds **11a-c** were confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic analysis (Scheme 3).



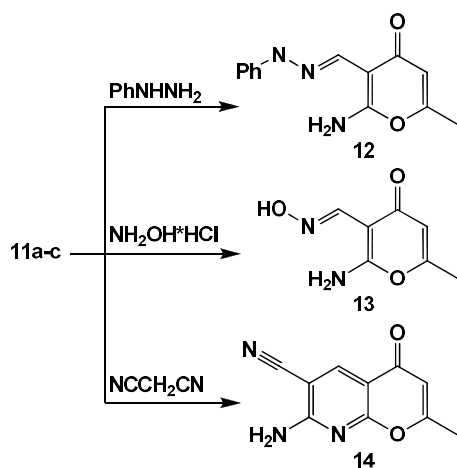
Scheme 2. Probable ways of formation of products **9** and **10**.



Scheme 3. Reduction of azolium salts **9a-c**.

The aldehyde nature of compounds **11a-c** was demonstrated by formation of the corresponding phenylhydrazone **12**, semicarbazone **13** and 7-amino-2-methyl-4-oxo-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile **14** upon their treatment with phenylhydrazine, semicarbazide and malononitrile, respectively. Preparation of the same products **12-14** starting from all the derivatives **11a-c** is a good

additional evidence for their structural assignments.



**Scheme 4.** Confirmation of aldehyde nature of derivatives 11a–c.

## Experimental part

### Material and methods

Nitriles **6a–c** were prepared according to the described procedures [13]. Other reagents were commercially available. All melting points were determined in open capillary tubes with a Thiele apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with a Bruker Avance 500 (500 MHz for  $^1\text{H}$  and 125 MHz for  $^{13}\text{C}$ ) spectrometer in  $\text{DMSO}-d_6$  solutions. Chemical shifts ( $\delta$ ) are given in ppm downfield from TMS as internal standard,  $J$  values are in Hz. The purities of all compounds were checked by  $^1\text{H}$  NMR spectroscopic analysis and by LC/MS analysis on an Agilent 1100 instrument.

### Synthesis

#### 2-Heterylidene-3,5-dioxohexanenitriles **8a–c**.

**General Procedure.** A solution of compound

**6a–c** (50 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**7**) (9.24 g, 65 mmol) in anhydrous dioxane (50 mL) was heated at reflux for 4 h. In the case of **6a** reaction was performed without solvent at 120 °C. After cooling, the reaction mixture was diluted with *i*-PrOH (80 mL) and the precipitate formed was filtered, washed with *i*-PrOH.

*2-(1,3-Dimethyl-1,3-dihydro-2*H*-benzimidazol-2-ylidene)-3,5-dioxohexanenitrile* (**8a**). Beige solid. Yield 91%, mp 89 °C.  $^1\text{H}$  NMR (mixture of keto/enol tautomers):  $\delta$  = 1.92 and 2.23 (2×s, 3 H,  $\text{CH}_3$ ), 3.71 (s, 1.4 H,  $\text{CH}_2$ -keto), 3.76 and 3.78 (2×s, 6 H, 2× $\text{NCH}_3$ ), 5.69 (br s, 0.3 H, CH-enol), 7.49–7.51 (m, 2 H, ArH), 7.77–7.79 (m, 2 H, ArH) ppm.  $^{13}\text{C}$  NMR:  $\delta$  = 22.1, 30.8, 33.3, 33.5, 54.8, 60.7, 95.5, 112.3, 121.2, 122.5, 125.3, 125.4, 132.3, 132.4, 151.8, 152.2, 174.8, 183.4, 186.0, 204.2 ppm.

*(2*E*)-2-(3-Methyl-1,3-benzothiazol-2(3*H*)-ylidene)-3,5-dioxohexanenitrile* (**8b**). Beige solid. Yield 86%, mp 208 °C.  $\delta$  = 2.03 and 2.24 (2×br s, 3 H,  $\text{CH}_3$ ), 3.92 (s, 1.6 H,  $\text{CH}_2$ -keto), 4.16 and 4.17 (2×s, 3 H,  $\text{NCH}_3$ ), 5.94 (br s, 0.2 H, CH-enol), 7.41–7.46 (m, 1 H, ArH), 7.57–7.62 (m, 1 H, ArH), 7.73–7.77 (m, 1 H, ArH), 7.96–8.00 (m, 1 H, ArH) ppm.  $^{13}\text{C}$  NMR:  $\delta$  = 22.1, 30.9, 36.3, 36.6, 54.7, 77.8, 96.2, 113.5, 119.6, 120.5, 122.8, 123.1, 125.1, 125.2, 126.7, 127.3, 127.9, 128.0, 140.3, 140.5, 165.2, 165.5, 177.2, 187.2, 187.5, 203.3 ppm.

(2E)-2-(3,4-Dimethyl-1,3-thiazol-2(3H)-ylidene)-3,5-dioxohexanenitrile (**8c**). Beige solid. Yield 88%, mp 148 °C. <sup>1</sup>H NMR (mixture of keto/enol tautomers):  $\delta$  = 1.96 and 2.19 (2xs, 3 H, CH<sub>3</sub>), 2.33 (s, 3 H, CH<sub>3</sub>), 3.81 (s, 1.5 H, CH<sub>2</sub>-keto), 3.90 (s, 3 H, NCH<sub>3</sub>), 5.79 (br s, 0.25 H, CH-enol), 7.01 and 7.04 (2xs, 1 H, ArH), 14.78 (s, 0.25 H, OH) ppm. <sup>13</sup>C NMR:  $\delta$  = 14.4, 14.5, 30.9, 36.7, 37.0, 54.4, 72.8, 76.0, 95.8, 108.7, 109.5, 120.2, 121.3, 140.3, 140.5, 164.5, 164.7, 175.1, 185.6, 186.4, 203.5 ppm.

#### Quaternary Salts 9a–c. General Procedure.

Compound **8a–c** (15 mmol) were dissolved in 40% HBr in acetic acid (30 mL, obtained by saturation of acetic acid with gaseous HBr) and the resulting solution was heated at reflux for 30 min. Upon cooling, the mixture was diluted with acetone (50 mL) and the solid precipitated was filtered, washed with cold acetone (10 mL).

2-(2-Bromo-4-hydroxy-6-methylpyridin-3-yl)-1,3-dimethyl-1H-benzimidazol-3-ium bromide (**9a**). Beige solid. Yield 95%, mp >250 °C. <sup>1</sup>H NMR:  $\delta$  = 2.51 (s, 3 H, CH<sub>3</sub>), 3.95 (s, 6 H, 2xNCH<sub>3</sub>), 7.02 (s, 1 H, PyH), 7.79–7.80 (m, 2 H, ArH), 8.12–8.16 (m, 2 H, ArH) ppm. <sup>13</sup>C NMR:  $\delta$  = 24.0, 33.0, 105.0, 105.9, 112.1, 114.3, 114.4, 127.8, 132.0, 141.1, 146.4, 167.4 ppm.

2-(2-Bromo-4-hydroxy-6-methylpyridin-3-yl)-3-methyl-1,3-benzothiazol-3-ium bromide (**9b**).

Beige solid. Yield 76%, mp 230 °C (dec). <sup>1</sup>H NMR:  $\delta$  = 2.48 (s, 3 H, CH<sub>3</sub>), 4.23 (s, 3 H, NCH<sub>3</sub>), 6.99 (s, 1 H, PyH), 7.93–7.96 (m, 1 H, ArH), 8.00–8.04 (m, 1 H, ArH), 8.42–8.47 (m, 1 H, ArH), 8.66–8.70 (m, 1 H, ArH) ppm. <sup>13</sup>C NMR:  $\delta$  = 23.7, 38.1, 110.1, 112.2, 112.8, 115.2, 118.6, 118.7, 122.7, 129.7, 129.8, 130.5, 130.6, 131.5, 131.6, 140.0, 141.4, 163.0, 166.8, 168.0, 169.6, 169.7 ppm.

2-(2-Bromo-4-hydroxy-6-methylpyridin-3-yl)-3,4-dimethyl-1,3-thiazol-3-ium bromide (**9c**).

Beige solid. Yield 88%, mp >250 °C. <sup>1</sup>H NMR:  $\delta$  = 2.45 (s, 3 H, CH<sub>3</sub>), 2.65 (s, 3 H, CH<sub>3</sub>), 3.83 (s, 3 H, NCH<sub>3</sub>), 6.90 (s, 1 H, PyH), 8.28 (s, 1 H, ArH) ppm. <sup>13</sup>C NMR:  $\delta$  = 14.3, 19.4, 38.1, 89.9, 101.7, 123.2, 147.5, 147.3, 159.8, 161.9, 164.9 ppm.

#### Quaternary Salts 10a–c. General Procedure.

Compound **8a–c** (15 mmol) were dissolved in the mixture of *i*-PrOH (40 mL) and HClO<sub>4</sub> (60%, 20 mL) and the resulting solution was heated at reflux for 30 min. Upon cooling, the mixture was diluted with acetone (50 mL) and the solid precipitated was filtered, washed with cold acetone (10 mL).

2-(2-Amino-6-methyl-4-oxo-4H-pyran-3-yl)-1,3-dimethyl-1H-benzimidazol-3-ium perchlorate (**10a**). Beige solid. Yield 90%, mp >250 °C. <sup>1</sup>H NMR:  $\delta$  = 2.28 (s, 3 H, CH<sub>3</sub>), 3.86 (s, 6 H, 2xNCH<sub>3</sub>), 6.08 (s, 1 H, ArH), 7.71 (br s, 2 H,

ArH), 8.06 (br s, 2 H, ArH), 8.28 (br s, 2 H, 2×NH) ppm. <sup>13</sup>C NMR: δ = 19.3, 32.6, 82.4, 110.3, 113.7, 126.7, 132.6, 146.8, 162.6, 164.5, 175.7 ppm.

*2-(2-Amino-6-methyl-4-oxo-4H-pyran-3-yl)-3-methyl-1,3-benzothiazol-3-ium perchlorate (10b)*. Beige solid. Yield 83%, mp >250 °C. <sup>1</sup>H NMR: δ = 2.28 (s, 3 H, CH<sub>3</sub>), 4.07 (s, 3 H, NCH<sub>3</sub>), 6.02 (s, 1 H, ArH), 7.78 (t, 1 H, J = 7.2 Hz, ArH), 7.86 (t, 1 H, J = 7.2 Hz, ArH), 8.23 (d, 1 H, J = 7.2 Hz, ArH), 8.37 (d, 1 H, J = 7.2 Hz, ArH), 12.01 (s, 1 H, NH) ppm. <sup>13</sup>C NMR: δ = 19.6, 96.7, 98.8, 117.3, 124.4, 128.4, 129.5, 130.2, 141.2, 153.7, 161.5, 169.3, 169.7 ppm.

*2-(2-Amino-6-methyl-4-oxo-4H-pyran-3-yl)-3,4-dimethyl-1,3-thiazol-3-ium perchlorate (10c)*. Beige solid. Yield 90%, mp >250 °C. <sup>1</sup>H NMR: δ = 2.22 (s, 3 H, CH<sub>3</sub>), 2.54 (s, 3 H, CH<sub>3</sub>), 3.73 (s, 3 H, NCH<sub>3</sub>), 6.02 (s, 1 H, ArH), 8.03 (s, 1 H, ArH), 8.14 (br s, 2 H, 2×NH) ppm. <sup>13</sup>C NMR: δ = 14.5, 19.2, 37.9, 87.81, 110.0, 120.8, 146.5, 162.2, 163.5, 175.2 ppm.

**Masked 2-Amino-6-methyl-4-oxo-4H-pyran-3-carbaldehydes 11a–c. General Procedure.** NaBH<sub>4</sub> (0.76 g, 20 mmol) was added in portions to an ice-cooled and stirred solution of the salt 10a–c (5 mmol) in aqueous MeOH (20 mL; MeOH–H<sub>2</sub>O, 7:3). After the addition was complete, the mixture was stirred at 0–5 °C for 1

h. The precipitate formed was filtered and washed with H<sub>2</sub>O.

*2-Amino-3-(1,3-dimethyl-2,3-dihydro-1H-benzimidazol-2-yl)-6-methyl-4H-pyran-4-one (11a)*. Beige solid. Yield 68%, mp 200–201 °C. <sup>1</sup>H NMR: δ = 2.15 (s, 3 H, CH<sub>3</sub>), 2.48 (s, 6 H, 2×NCH<sub>3</sub>), 5.29 (s, 1 H, CH), 5.84 (s, 1 H, ArH), 6.47–6.49 (m, 2 H, ArH), 6.61–6.63 (m, 2 H, ArH), 7.05 (br s, 2 H, NH<sub>2</sub>) ppm. <sup>13</sup>C NMR: δ = 19.0, 33.8, 84.5, 92.3, 107.4, 111.2, 119.7, 142.9, 160.1, 163.9, 178.1 ppm.

*2-Amino-6-methyl-3-(3-methyl-2,3-dihydro-1,3-benzothiazol-2-yl)-4H-pyran-4-one (11b)*. Beige solid. Yield 65%, mp 215 °C (dec). <sup>1</sup>H NMR: δ = 2.08 (s, 3 H, CH<sub>3</sub>), 2.61 (s, 3 H, NCH<sub>3</sub>), 5.66 (s, 1 H, CH), 6.39 (s, 1 H, ArH), 6.43 (d, 1 H, J = 7.6 Hz, ArH), 6.59 (t, 1 H, J = 7.6 Hz, ArH), 6.91 (t, 1 H, J = 7.6 Hz, ArH), 6.96 (d, 1 H, J = 7.6 Hz, ArH), 10.51 (s, 1 H, NH), 11.19 (s, 1 H, NH) ppm. <sup>13</sup>C NMR: δ = 18.9, 32.9, 73.5, 93.4, 109.1, 116.4, 118.8, 141.9, 148.7, 160.9, 166.0, 178.4 ppm.

*2-Amino-3-(3,4-dimethyl-1,3-thiazolidin-2-yl)-6-methyl-4H-pyran-4-one (11c)*. Beige solid. Yield 59%, mp 134–135 °C. <sup>1</sup>H NMR: δ = 1.23 (d, J = 4.2 Hz, 3 H, CH<sub>3</sub>), 2.37 (s, 3 H, NCH<sub>3</sub>), 2.76–2.93 (m, 2 H, SCH<sub>2</sub>), 3.11–3.18 (m, 1 H, NCH), 5.34 (s, 1 H, SCHN), 5.83 (s, 1 H, ArH), 6.48 (br s, 2 H, NH<sub>2</sub>). <sup>13</sup>C NMR: δ = 18.6, 19.2,

36.4, 37.0, 64.1, 74.0, 93.6, 107.9, 141.3, 161.1, 166.2 177.8 ppm.

*Phenylhydrazone 12 and Oxime 13.* A solution of compound **11a–c** (3.0 mmol) and phenylhydrazine hydrochloride (0.48 g, 3.3 mmol) or hydroxylamine hydrochloride (0.23 g, 3.3 mmol) in *i*-PrOH (10 mL) was heated at reflux under argon atmosphere for 2 h. After cooling, the mixture was poured into H<sub>2</sub>O (30 mL) and the solid that separated was filtered, washed with H<sub>2</sub>O (5 mL).

*2-Amino-6-methyl-4-oxo-4H-pyran-3-carbaldehyde phenylhydrazone (12).* Yields 73–80%, mp 100 °C. <sup>1</sup>H NMR: δ = 2.20 (s, 3 H, CH<sub>3</sub>), 5.88 (s, 1 H, ArH), 6.70 (t, 1 H, J = 7.6 Hz, Ph), 6.84 (d, 2 H, J = 7.6 Hz, Ph), 7.20 (t, 2 H, J = 7.6 Hz, Ph), 8.25 (s, 1 H, CH), 8.46 (d, 2 H, NH<sub>2</sub>), 10.00 (s, 1 H, NH) ppm. <sup>13</sup>C NMR: δ = 19.2, 94.8, 110.7, 111.8, 118.5, 129.6, 135.6, 145.9, 160.2, 162.0, 176.1 ppm.

*2-Amino-6-methyl-4-oxo-4H-pyran-3-carbaldehyde oxime (13).* Yields 64–71%, mp 100 °C. <sup>1</sup>H NMR: δ = 2.17 (s, 3 H, CH<sub>3</sub>), 5.86 (s, 1 H, ArH), 8.13 (br s, 2 H, NH<sub>2</sub>), 8.23 (s, 1 H, CH), 10.74 (s, 1 H, OH) ppm. <sup>13</sup>C NMR: δ = 19.1, 92.3, 110.6, 144.5, 160.5, 162.6, 176.1 ppm.

*7-Amino-2-methyl-4-oxo-4H-pyrano[2,3-b]pyridine-6-carbonitrile (14).* A mixture of compound **6a–c** (3.0 mmol), malononitrile (0.40 g, 6.0 mmol) and NH<sub>4</sub>Cl (0.02 g, 0.3 mmol) in

dioxane (10 mL) was heated at reflux for 4–5 h. After cooling, the precipitate formed was filtered, washed with H<sub>2</sub>O (5 mL) and recrystallized from DMF. Yields 38–47%, mp 100 °C. <sup>1</sup>H NMR: δ = 2.31 (s, 3 H, CH<sub>3</sub>), 6.13 (s, 1 H, ArH), 7.95 (br s, 2 H, NH<sub>2</sub>), 8.43 (s, 1 H, PyH) ppm. <sup>13</sup>C NMR: δ = 20.2, 90.8, 108.3, 110.5, 116.0, 143.6, 161.1, 163.0, 166.0, 176.0 ppm.

## Conclusions

To summarize, the present study has resulted in the first synthesis of masked 2-amino-6-methyl-4-oxo-4H-pyran-3-carbaldehydes. Aldehyde functionality has been brought into the 4H-pyran core in the form of a quaternary azolium salts. The synthetic potential of obtained unique masked aldehydes is not studied comprehensively to date and, therefore, further investigations in the field are in progress.

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