

Short Note

# 5-(5-Bromo-2-hydroxy-3-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol

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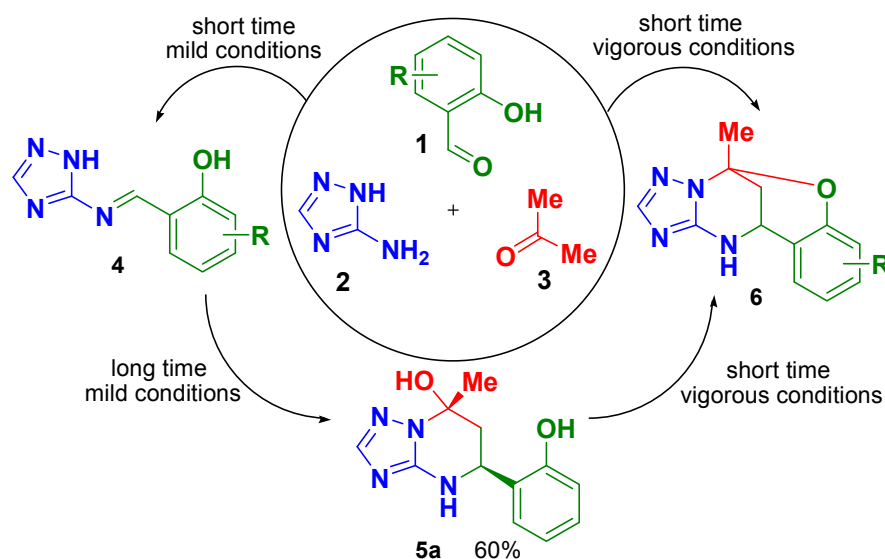
**Abstract:** The title compound was synthesized by multicomponent condensation of 3-amino-1,2,4-triazole, acetone and 5-bromo-2-hydroxy-3-methoxybenzaldehyde. The structure was established by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, IR spectroscopy and LC-MS.

**Keywords:** multicomponent reaction; MCR; Biginelli-like condensation

## 1. Introduction

Application of multicomponent reactions (MCRs) in organic synthesis is a powerful method to create a chemical complexity from simple starting building blocks [1–3]. The use of aminoazoles in MCRs as building blocks having two or more nonequivalent reaction centers is often associated with ambiguous selectivity of the process and different reaction outcomes depending on the reaction conditions applied [4–6]. In particular, Biginelli-like MCRs of 3-amino-1,2,4-triazole with aldehydes and  $\alpha$ -carbonyl CH-acids may result in several types of heterocyclic products (for a review see [7]). In our previous works we have shown that MCR of 3-amino-1,2,4-triazole (**2**) with acetone (**3**) and 2-hydroxybenzaldehydes (**1**) under acidic conditions leads to formation of different products, see Scheme 1. Under vigorous conditions, a series of oxygen-bridged compounds **6** was obtained with different substituents R, and only one example of open-bridge structure **5a** (R = H) was isolated in high yield under mild conditions [5].

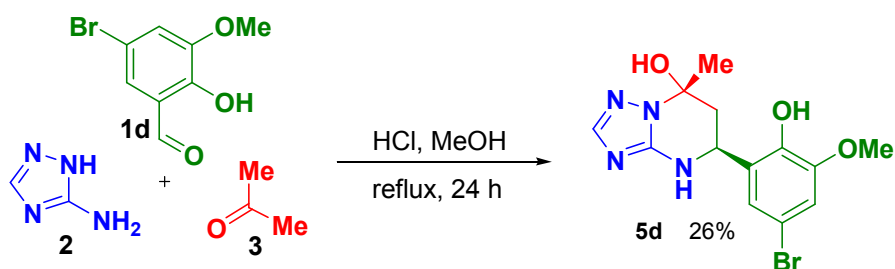
Here we aimed to examine the possibility of using different substituted 2-hydroxybenzaldehydes to obtain corresponding products **5b–h** with variable substituent R.



**Scheme 1.** Different products from the studied multicomponent reaction (MCR).

## 2. Results and Discussion

The 2-hydroxybenzaldehydes **1** with following substituents: 3-methoxy-(**1b**), 4-methoxy-(**1c**), 5-bromo-3-methoxy-(**1d**), 3-ethoxy-(**1e**), 5-bromo-(**1f**), 3,5-dibromo-(**1g**) and 4-hydroxy-(**1h**), were used in this study. In our first attempt, the conditions described in work [5] (40 °C, 16 h in the presence of HCl) were applied for aldehydes **1b–h** that resulted in formation of compounds **4** as the main product for all aldehydes as was determined by TLC. Further prolongation of the reaction up to 4 days at 40 °C led to formation of the desired product **5** only in the case of 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**1d**) but with a very small yield (18%). Reactions with other aldehydes resulted in formation of oxygen-bridged product **6** or its mixture with the desired product **5** and the azamethyne derivatives **4** as determined by <sup>1</sup>H-NMR spectra of precipitated products. Variation of reaction conditions, such as application of different solvents and acids (DMF, MeOH, water, acetic acid, trifluoroacetic acid, methylsulfuric acid), application of ultrasonic agitation and microwave irradiation under different temperatures did not improve the results, except for the case of aldehyde **1d**, where the desired product **5d** was obtained with moderate yield using MeOH and HCl under reflux conditions (Scheme 2).



**Scheme 2.** Synthesis of 5-(5-Bromo-2-hydroxy-3-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidin-7-ol, (5*R*,7*S*)- and (5*S*,7*R*)- racemic mixture (**5d**), relative configuration of stereogenic centers is shown.

The structure of the obtained product **5d** was established by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, IR spectroscopy and LC-MS. Relative configuration of the stereogenic centers in the molecule is given by analogy with earlier obtained unsubstituted open-bridged compound **5a** (R = H) and confirmed by NOE

experiments; structure of **5a** have been previously proven via single crystal X-ray diffraction study [5] (comparison of the NMR spectra is given in the supplementary materials).

To obtain 5-(5-Bromo-2-hydroxy-3-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**5d**) 10.0 mmol of 3-amino-1,2,4-triazole, 10.0 mmol of 5-bromo-2-hydroxy-3-methoxybenzaldehyde and 60.0 mmol (4.4 mL) of acetone in 25 mL of MeOH containing 625 mg HCl (15% solution in EtOH) were mixed in a round-bottom flask with condenser. The mixture was heated to reflux in oil bath for 24 h. After cooling and standing overnight the precipitate formed was filtered out and washed with 3 × 5 mL of MeOH and dried on air to give a cream-white powder with yield 26%.

Melting Point: 199–201 °C. LC-MS (APCI): Purity 99.3%; *m/z*: 355 (M + H<sup>+</sup>, Pos.), 353 (M – H<sup>+</sup>, Neg.). IR (KBr, cm<sup>-1</sup>): 3320 (OH), 3150 (CH, aromatic), 2943 (CH, aliphatic), 1634 (C=N), 1536, 1493 (C-C, C=C, NH bend), 1263, 1151, 1085 (C-C, C-O, C-N). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>, 400 MHz, ppm): δ 9.11 (s, 1H), 7.41 (s, 1H), 7.30 (s, 1H), 7.11–7.17 (m, 1H), 7.03–7.09 (m, 1H), 6.55 (s, 1H), 4.98–5.10 (m, 1H), 3.83 (s, 3H), 2.13–2.22 (m, 1H), 1.76–1.88 (m, 1H), 1.66 (s, 3H). <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>, 100 MHz, ppm): δ 154.0, 148.74, 148.70, 143.2, 130.8, 121.7, 113.9, 110.4, 80.5, 56.7, 44.8, 43.4, 27.1. Elemental Analysis: calcd. for C<sub>13</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 43.96; H, 4.26; N, 15.77. Found: C, 43.73; H, 4.34; N, 15.54.

**Supplementary Materials:** The supplementary materials and the molfile can be found at <http://www.mdpi.com/1422-8599/2016/2/M898>.

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**Author Contributions:** M.K., Y.V.S. and M.K.G. performed all the preliminary studies and the final experiment and analyzed the data, N.Yu.G. and Y.V.S. wrote the paper and composed the supplementary material, S.M.D. acted as the general supervisor.

**Conflicts of Interest:** The authors declare no conflict of interest.

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