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An efficient synthesis of novel 1,3-oxazolo[4,5-*d*]pyridazinones

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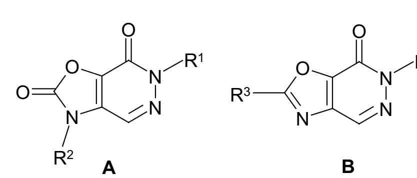
Abstract—A convenient and versatile synthetic approach to substituted 1,3-oxazolo[4,5-*d*]pyridazinones is developed. The oxazole ring was formed upon reaction of 5-amino-4-hydroxy-3(2*H*)-pyridazinone with various carboxylic acid derivatives using a microwave-assisted procedure, which favors the reaction time and purity of the resulting products. The developed methodology is suitable for rapid, parallel, automated synthesis of oxazolopyridazinone libraries.

Synthetic 3(2*H*)-pyridazinones are important scaffolds in drug discovery, with many of their analogs being used in the treatment of various human pathological states. They were described as nonsteroidal antiinflammatory drugs (e.g. Emorfazone and related compounds[1]), agents for therapeutic intervention of renal-urologic (e.g. FK-838[2]), cardiovascular (e.g. EMD-57283[3]), respiratory (e.g. NIP-502[4]), and dermatologic diseases (e.g. FR-181877[5]). According to these examples and due to evident structural similarity to many physiologically active heterocyclic-fused pyridazinones,[6] 1,3-oxazolo-[4,5-*d*]pyridazinones represent promising synthetic targets. Development of efficient synthetic approaches to the related combinatorial scaffolds will provide a valuable source of novel physiologically active agents.

To the best of our knowledge, only a few oxazolo[4,5-*d*]-pyridazines have previously been described. Thus, synthesis of 4-hydroxypyridazinones from the corresponding dicarboxylates has been reported.[7] A synthetic approach to oxazolo[4,5-*d*]pyridazin-2-ylacetamides has also been proposed, using reaction of *ortho*-amino-hydroxypyridazine with cyanoacetic acid amides at elevated temperatures.[8] Synthesis of several 2-substituted derivatives of oxazolo[4,5-*d*]pyridazine, such as 2-amino-7-chloroxazolo[4,5-*d*]pyridazine, was achieved by the cyclization of the corresponding N-pyridazin-5-ylformamide oximes.[9] 7-Chloro-2-phenyloxazolo[4,5-*d*]-pyridazine[10] and poly-2,6-oxazolo[4,5-*d*]pyridazine[11] were also reported. However, the described synthetic strategies have found limitations mainly due to lack of versatility and low yields of the desired products.

Here we report a convenient and versatile synthetic approach to novel 3,6-disubstituted 1,3-oxazolo[4,5-*d*]pyridazine-2(3*H*),7(6*H*)-diones of general formula **A** and 2,6-disubstituted 1,3-oxazolo[4,5-*d*]pyridazine-7(6*H*)-ones of general formula **B**.



5-Nitro-4-hydroxy-3(2*H*)-pyridazinones **6a**,**b** were prepared from the corresponding 4,5-dichloro derivatives **5a**,**b** using a previously reported procedure[12] (Scheme 1). Solutions of **5a**,**b** in N,N-dimethyl-formamide were treated with water solution of sodium nitrite to afford pure products in good yields (65–70%). The key intermediates, 5-amino-4-hydroxy-3(2*H*)-pyridazinones **7a**,**b**, were then prepared using a catalytic reduction of **6a**,**b**.

Keywords: 1,3-Oxazolo[4,5-*d*]pyridazinones; 5-Amino-4-hydroxy-3(2-*H*)-pyridazinone; Microwave-assisted; Rapid; Parallel; Automated synthesis.

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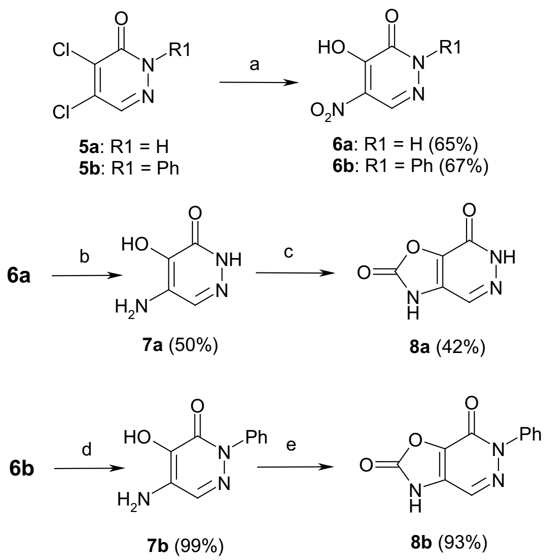
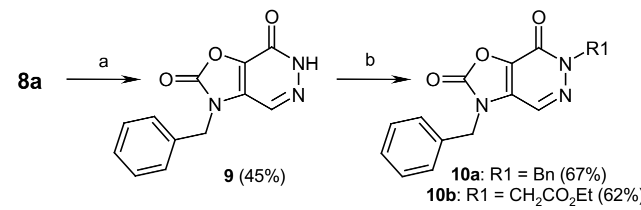


Scheme 1. Synthesis of 1,3-oxazolo[4,5-*d*]pyridazine-2(3*H*),7(6*H*)-diones. Reagents and conditions: (a) $NaNO_2$, $HCONMe_2/H_2O$, reflux, 5 h; (b) H_2/PtO_2, $EtOH/H_2O$, 50 °C, 10% Pd/C, 80 °C, reflux; (c) CDI, 1,4-dioxane, microwaves, 170 °C, 15 min; (d) $HCOONH_4$, 10% Pd/C, EtOH, reflux, 20 min; (e) CDI, 1,4-dioxane, reflux, 30 min.

A mild PtO_2-catalyzed hydrogenation of **6a** in 1:1 water–ethanol solution gave amine **7a** in 50% yield.[13] We have found these conditions to be optimal for synthesis of **7a**. At the same time, almost quantitative reduction of the nitro group of **6b** was achieved by using 5 equiv of ammonium formate and a catalytic amount of palladium on charcoal (10%) in ethanol for 15–20 min of heating under reflux (95% isolated yield of **7b**).

Access to 1,3-oxazolo[4,5-*d*]pyridazine-2(3*H*),7(6*H*)-diones **8a**,**b** was achieved by the reaction of 5-amino-4-hydroxypyridazinones **7a**,**b** with 1,1′-carbonyldiimidazole (CDI) (Scheme 1). It should be noted that our attempts to obtain **8a** from **7a** and CDI using traditional (nonmicrowave) thermal conditions led to a complex mixture of products. Only the microwave-assisted procedure afforded the desired product. The yield of the isolated **8a** was 42%. At the same time, reaction of **7b** with CDI proceeded rapidly, with higher yield (93%) and did not require microwave assistance.

Compounds **8a** and **8b** were found to be useful precursors for a variety of novel N3- and N6-substituted 1,3-oxazolo[4,5-*d*]pyridazine-2(3*H*),7(6*H*)-dione derivatives, which were obtained in good yields from **8a** and **8b** by reaction with appropriate electrophilic agents. As we observed the NH-group at the position 3 in **8a** is relatively more active compared to NH- in the position 6. Thus N3-benzyl derivative **9** was prepared from **8a** and stoichiometric quantity of benzyl bromide in the presence of cesium carbonate and in N-methylpyrrolidone at the room temperature (Scheme 2).[14] Subsequent reaction of **9** with electrophilic agents, such as benzyl bromide or ethyl chloroacetate, conducted at the same conditions, but at a higher temperature and using some excess of alkylating agents led to the N3,N6-disubstituted compounds **10a**,**b** in good yields.

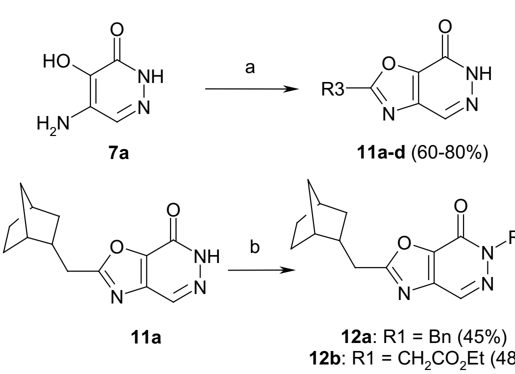


Scheme 2. Reagents and conditions: (a) $PhCH_2Br$, N-methylpyrrolidone, Cs_2CO_3, 20 °C, 4–6 h; (b) BnBr (**10a**) or $ClCH_2CO_2Et$ (**10b**), N-methylpyrrolidone, Cs_2CO_3, 50 °C, 6–10 h.

All new 1,3-oxazolo[4,5-*d*]pyridazine-2(3*H*),7(6*H*)-diones were characterized by ^1H NMR, LCMS, and HRMS spectral data.[15]

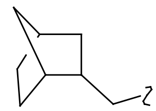
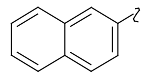
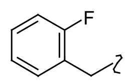
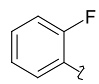
Reaction of *o*-aminophenols with carboxylic acids or their derivatives, such as acid chlorides, anhydrides, esters, amides or nitriles, under thermal conditions is a known method for the preparation of substituted benzoxazoles.[16] In the present work, we demonstrate the utility of this approach to provide some substituted 1,3-oxazolo[4,5-*d*]pyridazine-7(6*H*)-ones. 5-Amino-4-hydroxy-3(2*H*)-pyridazinone **7a** was used as a starting compound for microwave-assisted formation of a series of novel oxazolopyridazinones **11a**–**d** (Scheme 3). A mixture of **7a** with the corresponding carboxylic acid in N-methylpyrrolidone with addition of polyphosphoric acid was irradiated in the microwave reactor[17] at 230 °C for 15–20 min to afford a series of 2-substituted oxazolopyridazinones **11a**–**d**[18] with 60–80% yields (Table 1). There was observed clear advantage in using microwave assistance for this reaction. The yields under microwaves were considerable higher, compared to that observed under traditional thermal conditions (based on LCMS data).

The resulting 2-substituted oxazolopyridazinones can be alkylated with the appropriate alkylating agents under the reaction conditions similar to those described for Scheme 2.[14] For instance, 2-bicyclo[2.2.1]hept-2-yl-methyl derivative **11a** was converted in 45–50% yields into N6-substituted oxazolopyridazinones **12a**,**b** upon the treatment with benzyl bromide or ethyl chloroace-



Scheme 3. Reagents and conditions: (a) R3-COOH, 15 wt % H_3PO_4 in N-methylpyrrolidone, microwaves, 230 °C, 15–20 min. (b) BnBr (**12a**) or $ClCH_2CO_2Et$ (**12b**), N-methylpyrrolidone, Cs_2CO_3, 30–50 °C, 2 h.

Table 1. Substituted 1,3-oxazolo[4,5-*d*]pyridazine-7(6*H*)-ones **11a–d** (Scheme 3)

Compound	R	Yield (%)
11a		75
11b		81
11c		63
11d		77

tate respectively, in the presence of cesium carbonate in N-methylpyrrolidone (Scheme 3).

In summary, we have reported a new convenient approach to a variety of substituted 1,3-oxazolo[4,5-*d*]-pyridazinones, using the reaction of 5-amino-4-hydroxy-3(2*H*)-pyridazinone with various carboxylic acid derivatives. Optimization of the synthetic route was achieved by using a microwave-assisted methods, which have received an increasing interest in organic synthesis.[19] The developed methodology is suitable for rapid, parallel, automated synthesis of oxazolopyridazinone libraries, which are of interest as promising structural analogs of biologically active pyridazinones.

1. Typical procedures for the microwave-assisted synthesis of substituted 1,3-oxazolo[4,5-*d*]pyridazinones

1.1. 1,3-Oxazolo[4,5-d]pyridazine-2(3*H*),7(6*H*)-dione (8a)

A mixture of **7a** (0.541 g, 4.26 mmol), and 1,1′-carbonyldiimidazole (0.770 g, 4.8 mmol) in 1,4-dioxane (6 mL) was irradiated in microwave reactor at 170 °C for 15 min. The reaction mixture was cooled, the precipitate was filtered off and recrystallized (1,4-dioxane/water, 9:1) to afford **8a** in 42% yield.

1.2. 2-Substituted 1,3-oxazolo[4,5-*d*]pyridazine-7(6*H*)-ones (11a–d)

A mixture of **7a** (0.254 g, 2 mmol) and the corresponding acid R3-COOH (3 mmol) in 0.5 mL of 15% polyphosphoric acid solution in N-methylpyrrolidone was irradiated in microwave reactor at 230 °C for 15 min. Then, the reaction mixtures were cooled and dissolved in a minimal amount of dimethylsulfoxide. Water (5 mL) was added and the mixtures were extracted with dichloroethane (3 × 5 mL). The combined organic layers were washed with water (2 × 5 mL) and aqueous sodium bicarbonate (5%, 5 mL), dried, filtered, and concentrated in vacuo to give **11a–d**. Purification of the residues by flash column chromatography (silica gel, 5–50% THF–dichloromethane) afforded pure **11a–d** in 60–80% yields.

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14. Alkylation was carried out using the following typical procedure: A solution of benzyl bromide (1 mmol) in dioxane (0.5 mL) was added to a mixture of **8a** (1 mmol) and Cs_2CO_3 (500 mg) in N-methylpyrrolidone (1 mL). The reaction mixture was stirred at 20 °C for 4–6 h. After that time, the LCMS analysis of the reaction mixture indicated the monoalkylated derivative **9** as a major product. The di-alkylated derivative **10a** was observed in trace amounts. The reaction mixture was diluted with water (5 mL), and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was dried and concentrated in vacuo. Flash column chromatography of the residue (silica gel, CH_2Cl_2–THF, 2:1) provided pure **9** (152 mg, 45%). Compound **10a** was obtained from the mono-alkylated derivative **9** by the reaction with 1.5 equiv of benzyl bromide at 50 °C for 6–10 h using the above described procedure. Other alkylation products described in this report were prepared by the similar procedures.

15. Selected data: Compound **8a**: LCMS m/z 154 (M + 1); High resolution MS data (HRMS): determined by the MALDI-FTMS method: $M+23^{+}$ 176.0073 (expected 176.0067). Compound **8b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.4–7.5 (m, 5H), 8.33 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 126.3, 126.4, 128.7, 129.1, 131.8, 135.5, 141.5, 150.8, 153.8; LCMS m/z 230.0 (M + 1). Compound **9**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.04 (s, 2H), 7.28–7.44 (m, 5H), 8.31 (s, 1H), 13.46 (br s, 1H); LCMS m/z 244 (M + 1). HRMS: MH^{+} 244.0720 (expected 244.0717). Compound **10a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.04 (s, 2H), 5.33 (s, 2H), 7.35–7.45 (m, 10H), 8.38 (s, 1H); HRMS: LCMS m/z 334 (M + 1); HRMS: MH^{+} 334.1183 (expected 334.1186). Compound **10b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18 (t, J = 7.5 Hz, 3H), 4.08 (q, 7.5 Hz, 2H), 4.95 (d, J = 1.7 Hz, 2H), 5.05 (s, 2H); 7.30–7.45 (m, 5H), 8.37 (s, 1H); LCMS m/z 330 (M + 1); HRMS: MH^{+} 330.1083 (expected 330.1084).

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17. Parallel solution-phase reactions were performed using a laboratory synthesizer 'CombiSyn-012-3000' (Baru, M.; Ivachtchenko, A. Russian Patent 2180609, 2002; Patent PCT WO 02/087740 A1, 2002; *Chem. Abstr.* **2003**, *138*, 014907f).

18. Satisfactory analytical data (^{1}H NMR and MS) were obtained for compounds **11a–d**. Selected data: Compound **11a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02–1.21 (m, 4H), 1.36–1.54 (m, 4H), 1.94–2.04 (m, 2H), 2.20 (br s, 1H), 2.77–2.99 (m, 2H), 8.51 (s, 1H), 13.35 (br s, 1H); LCMS m/z 246 (M + 1); HRMS: MH^{+} 246.1238 (expected 246.1237). Compound **11b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60–7.70 (m, 2H), 7.98–8.22 (m, 4H), 8.61 (s, 1H), 8.81 (s, 1H), 13.43 (br s, 1H); LCMS m/z 264 (M + 1); HRMS: MH^{+} 264.0767 (expected 264.0767). Compound **11c**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.49 (s, 2H), 7.02–7.11 (m, 1H), 7.21–7.30 (m, 2H), 7.35–7.45 (m, 1H); 8.51 (s, 1H), 13.45 (br s, 1H); LCMS m/z 246 (M + 1); HRMS: MH^{+} 246.0674 (expected 246.0673).

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