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A NEW EFFICIENT SYNTHESIS OF 5-ARYLOXAZOLES FROM ARYLIDENE DIACETATES AND APPLICATION TO THE PREPARATION OF BMS-337197, A NOVEL IMPDH INHIBITOR

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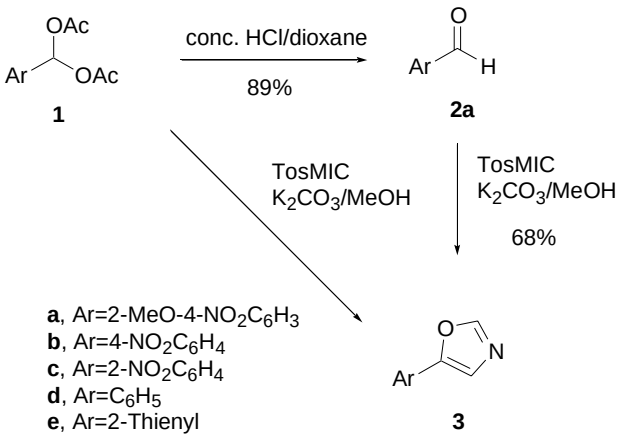
Abstract – A new method for the synthesis of 5-aryloxazoles is described. Treatment of arylidene diacetates with one equivalent of TosMIC reagent in the presence of excess of potassium carbonate in methanol afforded 5-aryloxazoles in "one-pot" in 90-94%. Heteroarylidene diacetates reacted in a similar way. Application of the new method to the synthesis of the novel IMPDH inhibitor BMS-337197 is also presented.

p-Tosylmethyl isocyanide (TosMIC) is a versatile reagent in organic synthesis.[1] It is particularly useful in the synthesis of azoles such as oxazoles, imidazoles, thiazoles, 1,2,4-triazoles, pyrroles and others.[1,2] Recently, we extended the application of TosMIC reagent to the synthesis of 1-arylimidazole-5-carboxylates[2a,2d] and imidazo[1,5-*a*]quinoxalin-4-ones,[2b-d] both important intermediates for the preparation of biologically important and medicinally useful agents.

In the course of our study towards the discovery of the novel inosine monophosphate dehydrogenase (IMPDH) inhibitor BMS-337197 and others,[3,4] we required an easy access to large amounts of 5-(2-methoxy-4-nitrophenyl)oxazole (**3a**).[4] This compound was previously prepared in a stepwise fashion from 2-methoxy-4-nitrobenzylidene diacetate (**1a**) in 61% overall yield with a key step being TosMIC mediated oxazole formation through aldehyde (**2a**) (Scheme 1).[5] Thus, acidic hydrolysis of **1a** with concentrated HCl in dioxane under reflux overnight afforded 2-methoxy-4-nitrobenzaldehyde (**2a**) in 89% yield. Subsequent reaction of **2a** with TosMIC reagent in methanol using potassium carbonate as base gave **3a** in 68% yield.[5,6] While this stepwise method can be used to prepare the desired compound (**3a**),

we envisioned that this synthesis could be improved by direct treatment of the arylidene diacetate with TosMIC reagent. Under the reaction conditions, the diacetates (**1**) are expected to undergo basic hydrolysis, giving rise to aldehydes (**2**) *in situ* which in turn would react with TosMIC reagent to give oxazole products (**3**). A similar strategy has been recently used in our synthesis of 1-arylimidazole-5-carboxylates.[2a,2d]

Scheme 1



Indeed, treatment of **1a** with three equivalents of potassium carbonate in the presence of one equivalent of TosMIC reagent in methanol at 55°C for 15 min afforded cleanly the desired product (**3a**).[4] Compound (**3a**) was readily isolated in 91% yield by crystallization after quenching the reaction with water. Compared to the original stepwise preparation of **3a**, the new "one-pot" method not only shortened the synthesis, but also improved the overall yield by 30% (91% vs 61%).

To determine if this new reaction of TosMIC reagent is general, several commercially available arylidene diacetates (**1b**-**e**)[7,8] were subjected to the above reaction conditions and the results are summarized in Table 1.

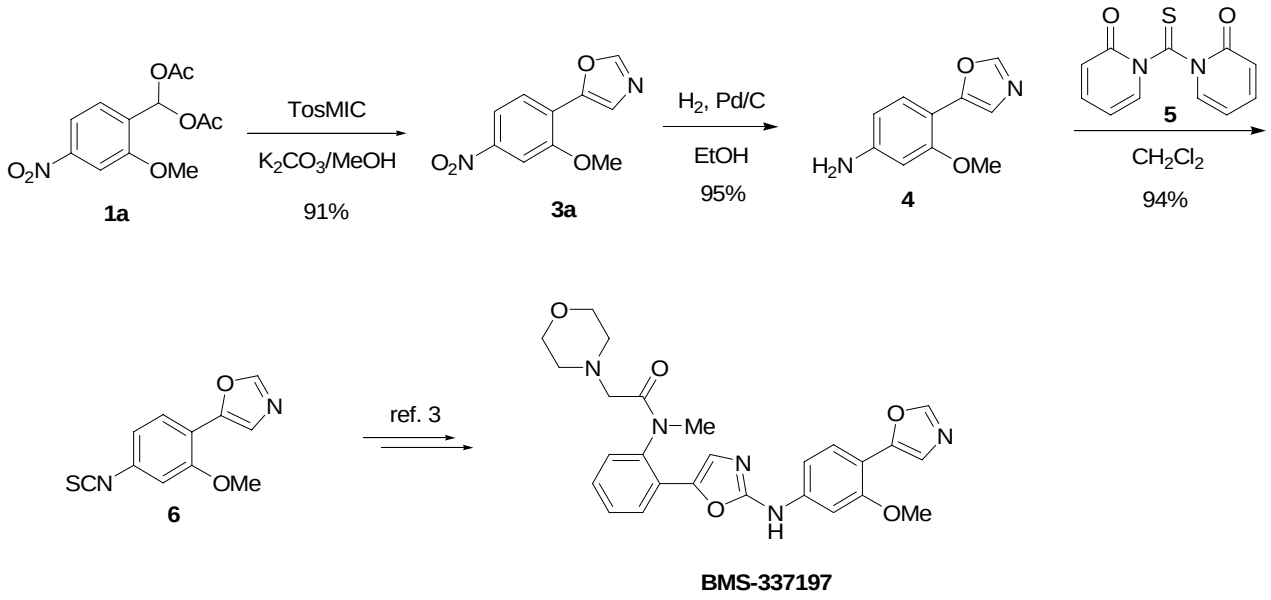
Table 1. Preparation of 5-Aryloxazoles (**3**) *via* Reaction of TosMIC Reagent with Arylidene Diacetates (**1**):

Entry	Ar	Time (h)	**3** Yield (%)[a,b]
1	2-MeO-4-$NO_2C_6H_3$	0.25	91[68][4]
2	4-$NO_2C_6H_4$	0.25	90[91][9]
3	2-$NO_2C_6H_4$	0.25	92[42][10]
4	C_6H_5	1.75	90[91][9]
5	2-Thienyl	16.0	94[80][11]

[a]Isolated yields for the new "one-pot" synthesis. [b]Yields in [ ] are those reported in the literature.

As can be seen from Table 1, the new reaction of TosMIC works with benzylidene diacetates (**1a-d**) as well as heteroarylidene diacetate (**1e**). Compared to the reactions of TosMIC reagent with aldehydes reported in the literature, the new reaction gave improved or comparable yields for all the desired oxazole products. With compound (**3a**) readily accessible from the diacetate (**1a**), the next step was the nitro group reduction to give the corresponding aniline (**4**) (Scheme 2).[4] Thus, treatment of **3a** in ethanol with 10% palladium on charcoal under 35-45 psi hydrogen smoothly gave **4** in 95% isolated yield. Reaction of aniline (**4**) with 1,1'-thiocarbonyldi-2(2*H*)-pyridone (**5**) in methylene chloride at room temperature for 3 h afforded 3-methoxy-4-(5-oxazolyl)phenyl isothiocyanate (**6**) in 94% yield after silica gel chromatographic separation, which was further elaborated to BMS-337197, our newly discovered IMPDH inhibitor.[3]

Scheme 2



In summary, an improved method for the synthesis of 5-(2-methoxy-4-nitrophenyl)oxazole, an important intermediate in the synthesis of biologically active compounds,[3,4] has been developed. The new method involved a direct reaction of TosMIC reagent with arylidene diacetate in a "one-pot" fashion and could be readily carried out in multigram scale. In addition, the new reaction of TosMIC is general for both arylidene and hetreoarylidene diacetates, giving 5-substituted oxazoles in >90% yields. While 5-aryloxazoles could be prepared from aldehydes and TosMIC reagent in many cases, the new method is particularly advantageous for those occasions where the aldehydes need to be prepared from arylmethanes through arylidene diacetate intermediates. Furthermore, the new method was successfully used in the preparation of BMS-337197, our newly discovered IMPDH inhibitor.

EXPERIMENTAL

Preparation of 5-aryloxazoles 3, general procedure: In a 100 mL rounded bottom flask was added

arylidene diacetate (**1**, 10 mmol), TosMIC reagent (2.0 g, 10.4 mmol), K_2CO_3 (4.4 g, 31.6 mmol) and MeOH (30 mL). The reaction mixture was heated to 55°C and stirred under argon for 15 min to 16 h when HPLC showed the reaction was complete (Table 1). Water (30 mL) was added and the resulting slurry was cooled to rt. The solids were filtered, washed with water (3x5 mL) and dried in a vaccum oven at 50°C to give **3**. Analytical samples (**3a-d**) were obtained by recrystallization from dichloromethane and hexane.

5-(2-Methoxy-4-nitrophenyl)oxazole (3a): 91%; mp 151-152 °C (from CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.92 (m, 2H), 7.85 (s, 1H), 7.77 (s, 1H), 4.10 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 155.5, 150.8, 147.8, 146.2, 128.6, 126.0, 122.9, 116.3, 106.1, 56.2. Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.28; H, 3.42; N, 12.35.

5-(4-Nitrophenyl)oxazole (3b): 90%; mp 136-138 °C (from CH_2Cl_2/hexane), lit.,[9] mp 136-138.5 °C. The spectroscopic data were consistent with the structure of the product.

5-(2-Nitrophenyl)oxazole (3c): 92%; mp 77.5-79.5 °C (from CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.45-7.50 (m, 1H), 7.58-7.62 (m, 1H), 7.65-7.67 (m, 1H), 7.78-7.81 (m, 1H), 7.91 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 152.0, 148.2, 132.9, 130.1, 130.0, 126.2, 124.8, 122.0. Anal. Calcd for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.65; H, 2.99; N, 14.89.

5-Phenyloxazole (3d): 90%; mp 38-40 °C (from CH_2Cl_2/hexane), lit.,[9] mp 36-38 °C. The spectroscopic data were consistent with the structure of the product.

5-(2-Thienyl)oxazole (3e): 94%; oil. ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.16 (d, J=1.2 Hz, 1H), 7.14 (d, J=3.5 Hz, 1H), 7.05 (s, 1H), 6.90 (dd, J=1.2 Hz, J=3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 149.8, 146.9, 129.5, 127.8, 125.8, 124.6, 121.1. HRMS Calcd for C_7H_5NOS (M^++H): 152.0170. Found: 152.0172.

5-(2-Methoxy-4-aminophenyl)oxazole (4): In a 2 L hydrogenation flask was placed **3a** (130.0 g, 0.6131 mol), Pd/C (10%, 26.2 g) and dry EtOH (1280 mL). The mixture was hydrogenated at 35-45 psi H_2 until the reaction was complete. The mixture was filtered over a pad of celite (20 g) and the cake was washed with EtOH (3x100 mL). The filtrate was concentrated to a volume of 350 mL. Heptane (500 mL) was added to the resulting slurry. After stirring for 2 h at rt, the slurry was filtered. The cake was washed with heptane (3x100 mL) and dried to give **4** (80.0 g). A second portion of product (30.2 g) was recovered from the mother liquor affording a total yield of 95%. mp 114.5-116.5 °C (from CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.41 (s, 1H), 6.41 (dd, J=8.4, 2.1 Hz, 1H), 6.34 (d, J=2.1 Hz, 1H), 3.98 (br s, 2H), 3.94 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 55.7, 98.4, 107.7, 108.3, 123.0, 126.6, 148.4, 148.9, 149.0, 157.5. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.03; H, 5.44; N, 14.85.

5-(4-Isothiocyanato-2-methoxyphenyl)oxazole (6): In a 250 mL rounded bottom flask was placed **4**

(3.50 g, 18.4 mmol), 1,1'-thiocarbonyldi-2(2*H*)-pyridone (**5**) (4.41 g, 18.4 mmol) and methylene chloride (100 mL). The reaction mixture was stirred under argon at rt for 3 h. The solvent was evaporated under vacuum and the residue was subjected to column chromatography (30% AcOEt/hexane) to afford **6** (4.02 g, 94%) as white crystals. mp 116-117.5 °C. ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.57 (s, 1H), 6.93 (dd, J=8.4, 1.8 Hz, 1H), 6.81 (dd, J=1.8 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 55.9, 108.5, 116.4, 118.4, 126.1, 126.7, 131.6, 136.2, 147.0, 149.8, 156.1. Anal. Calcd for $C_{11}H_8N_2O_2S$: C, 56.88; H, 3.47; N, 12.06; S, 13.80. Found: C, 56.61; H, 3.20; N, 12.10; S, 13.56.

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