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Reinvestigation of Mucohalic Acids, Versatile and Useful Building Blocks for Highly Functionalized α,β-Unsaturated γ-Butyrolactones

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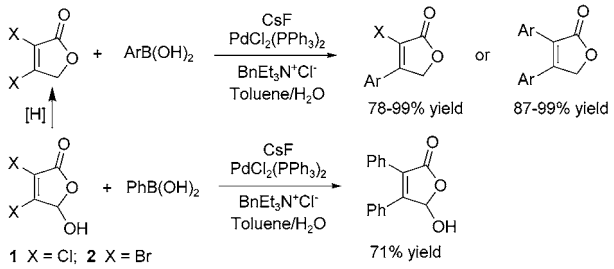
ABSTRACT



Mucohalic acids (mucochloric acid (1, 3,4-dichloro-5-hydroxy-5*H*-furan-2-one) and mucobromic acid (2, 3,4-dibromo-5-hydroxy-5*H*-furan-2-one)) are inexpensive, commercially available starting materials with multiple functional groups. These compounds have been modified by way of reduction followed by Suzuki cross-coupling reactions involving arylboronic acids to afford highly functionalized α,β-unsaturated γ-butyrolactones in excellent yield. The synthetic utility of these building blocks was effectively demonstrated through preparation of the antiinflammatory drug Vioxx.

Mucohalic acids (mucochloric acid (**1**, 3,4-dichloro-5-hydroxy-5*H*-furan-2-one) and mucobromic acid (**2**, 3,4-dibromo-5-hydroxy-5*H*-furan-2-one)) are inexpensive, commercially available starting materials with multiple functional groups. Mucochloric acid has been known for more than 100 years and was first prepared in 1890 from β,γ-dichloropyromucic acid and bromine water,[1a] later by heating furfural with manganese dioxide and hydrochloric acid (1899),[1b] and more recently by chlorination of butyne-1,4-diol (1960).[1c] These four-carbon molecules have seen limited use[2] in organic synthesis, presumably for reasons associated with the many reactive sites, poor stability under basic conditions, and assumed difficulty in the selective manipulation of the halogen atoms. However, these two highly functionalized molecules are very attractive as potential useful building blocks in synthesis because they can be viewed as α,β-unsaturated acids, α,β-unsaturated aldehydes, fully substituted (*Z*)-olefins, vinyl halides, masked hemiacetals, or pseudo lactones. The ever-increasing importance of transition metal-catalyzed cross-coupling reactions[3] has driven us to apply this chemistry to these intriguing structures and explore this untapped chemical resource. Herein we report a means of selectively manipulating these densely functionalized molecules through Suzuki cross-coupling reactions.

Recently, we reported the first direct reductive amination of mucohalic acids to prepare highly functionalized α,β-unsaturated γ-butyrolactams and γ-amino acids.[4] Interest-

(1) (a) Hill, H. B.; Jackson. O. R. *Am. Chem. J.* **1890**, *12*, 37. (b) Simonis, H. *Ber*. **1899**, *32*, 2085. (c) Dury, K. *Angew. Chem*. **1960**, *72*, 864.

(2) (a) Wasserman, H. H.; Precopio, F. M. *J. Am. Chem. Soc*. **1954**, *76*, 1242 and references therein. (b) Fishbein, P. L.; Moore, H. W. *Org. Synth.* **1990**, *69*, 205. (c) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem*. **2000**, *65*, 337.

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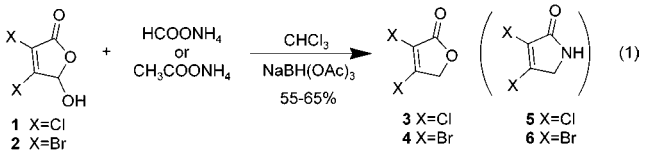
ingly, attempted reductive aminations of mucohalic acids with ammonium formate or ammonium acetate as the NH_3 equivalent failed to give expected lactams **5** and **6**, but rather lactones **3** and **4** were isolated (Scheme 1).[5] This serendipitous finding led us to investigate the chemical behavior of these lactones.

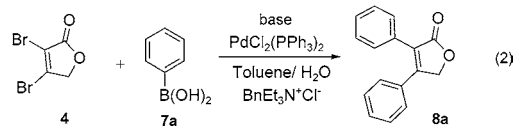
Scheme 1. Attempted Reductive Aminations of Mucohalic Acids



Both γ-butyrolactones and α,β-unsaturated γ-butyrolactones have attracted considerable attention due to their interesting biological properties and ubiquitous nature.[6] For example, (−)-arctigenin is a bisbenzylbutyrolactone that exhibits anti-HIV properties,[7] and the antiinflammatory Vioxx[8] and the vasodilator Eucilat[9] are pharmaceutical agents; monomeric substance **8a** is used in polymer science. Although it has been reported that the marine antibiotics rubrolides C and E were synthesized by palladium(0)-catalyzed cross-coupling of bromobutenolides with arylboronic acids[10] and that Bellina and Rossi have converted lactone **4** to unsymmetric 3,4-disubstituted and 4-substituted 5*H*-furan-2-ones, such as cytotoxic rubrolide M,[11] we decided to study carbon−carbon bond formation of **3** and **4** in the form of a bis-Suzuki cross-coupling reaction. Suzuki cross-coupling reactions are commonly used and amenable to a combinatorial approach to early lead development in drug discovery.

The reaction between lactone **4** and phenylboronic acid (**7a**) was examined initially.[12] The choice of base in our system was a key issue because carrying out the coupling reaction under strongly basic conditions would result in side reactions such as hydrolysis of the γ-lactone, ring opening, or bromide-hydroxyl exchange if a homogeneous system was employed. We believed that using phase-transfer methodology[13] would favor the desired palladium insertion (in the organic layer) and minimize unwanted side reactions (in the aqueous layer). Results of a base screen (Table 1) suggested that CsF and KF promoted the coupling reactions to give good yields (Table 1, entries 7 and 8) under very mildly basic conditions. These results are consistent with Wright's finding[14] that fluorides are valuable and advantageous in boronic acid coupling reactions. Extending the reaction time to 24 h resulted in an 88% yield of compound **8a** (Table 1, entry 9).

Table 1. Suzuki Coupling Using Different Bases[a]



entry	base (reaction time)	yield[b] (%)
1	K_3PO_4 (2 h)	56
2	K_2CO_3 (3 h)	42
3	Cs_2CO_3 (3 h)	51
4	Na_2CO_3 (3 h)	41
5	$NaHCO_3$ (3 h)	68
6	K_2HPO_4 (3 h)	68
7	KF (3 h)	71
8	CsF (3 h)	78
9	CsF (24 h)	88

[a] Reaction conditions: 2.5 mmol of **4**, 2.4 equiv of **7a**, 4.0 equiv of base, 5 mol % $PdCl_2(PPh_3)_2$, 5 mol % $BnEt_3N^+Cl^-$, reflux. [b] Isolated yield after chromatography.

Success with the coupling reaction between **7a** and **4** prompted us to explore the possibility of coupling **7a** with **3**. The use of chlorides in Suzuki coupling reactions has encountered significant difficulty, which has only recently been overcome.[15] In view of its lower cost and the greater synthetic challenge that it posed, lactone **3** was employed in

(4) Zhang, J.; Blazecka, P. G.; Davidson, J. G. Patent pending.

(5) (a) Lalonde reported preparation of **3** from mucochloric acid: Lalonde, R. T.; Perakyla, H.; Cook, G. P.; Dence, C. W. *Environ. Toxicol. Chem.* **1990**, *9*, 687. (b) Rossi reported that **4** was prepared in 75% yield by reduction of mucobromic acid by $NaBH_4$: Rossi, R.; Bellina, F.; Raugei, E. *Synlett*. **2000**, *12*, 1749.

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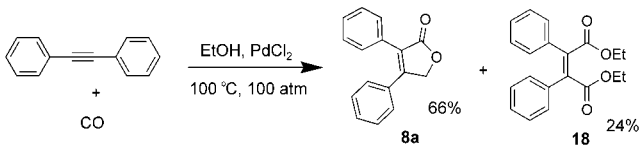
(10) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett*. **1998**, *39*, 7665.

(11) (a) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett*. **2002**, *43*, 2023. (b) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett*. **2001**, *42*, 3851. (c) Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2000**, *57*, 9997.

(12) Diphenylbutyrolactone **8a** was once produced by the carbonylation of diphenylacetylene in ethanol using $PdCl_2$/HCl under 100 atm at 100 °C. This process generated a significant amount of diethyl diphenylmaleate (**18**) as side product. See: Tsuji, J.; Nogi, T. *J. Am. Chem. Soc*. **1966**, *88*, 1289.



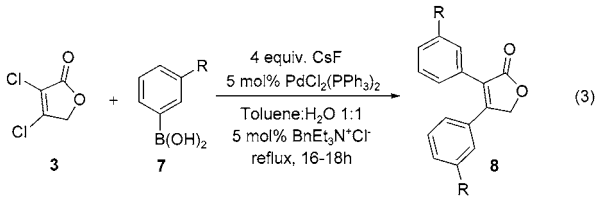
(13) For lead references on the use of phase-transfer methodology in palladium-catalyzed carbon−carbon bond-forming reactions, see: (a) Jeffrey, T. *Tetrahedron Lett.* **1994**, *35*, 3051. (b) Jeffrey, T.; Galland, J.-C. *Tetrahedron Lett.* **1994**, *35*, 4103. (c) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *J. Org. Chem.* **2000**, *65*, 3107. (d) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910. (e) Wang, J.-X.; Liu, Z.; Hu, Y.; Wei, B.; Bai, L. *Synth. Commun.* **2002**, *32*, 1607.

(14) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

the Suzuki reaction. The coupling of **7a** with **3** was very successful under our reaction conditions, and lactone **8a** was isolated in 93% yield without need of any special ligands.[15b−g]

Equation 3 (Table 2) represents by far a superior means

Table 2. Suzuki Coupling of **3** with Different Arylboronic Acids[a]



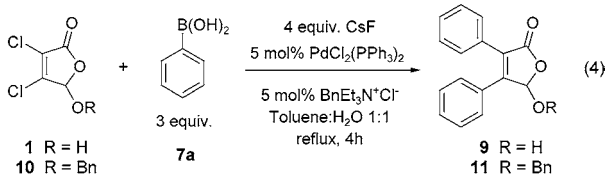
entry	R	8	yield[b] (%)
1	H	**8a**	93
2	CH_3	**8b**	87
3	OMe	**8c**	94
4	Cl	**8d**	89
5	F	**8e**	89
6	CF_3	**8f**	99

[a] Reaction conditions: 1.8−2.5 mmol of **3**, 3.0 equiv of **7**, 4.0 equiv of CsF, 5 mol % $PdCl_2(PPh_3)_2$, 5 mol % $BnEt_3N^+Cl^-$, reflux, 16−18 h. [b] Isolated yield after chromatography.

of producing **8a**. It employs very mild conditions, affords product in excellent chemical yield, and is devoid of significant side reactions. The reaction has been further extended to encompass several differently substituted arylboronic acids (Table 2) with excellent results.

To further the synthetic utility of this bis-Suzuki reaction, mucochloric acid (**1**) was used in the direct coupling with phenylboronic acid (**7a**), and product **9** was isolated in 71% yield (Scheme 2). When benzylacetal **10** was used in the

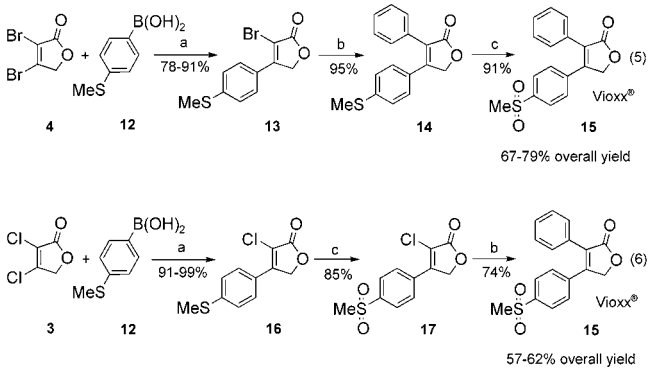
Scheme 2. Suzuki Coupling of Mucochloric Acid



coupling, product **11** was isolated in 90% yield.

Regioselective monoarylation of **3** and **4** is very important, and the products are useful as building blocks for preparing more complex molecules. Although it was reported[5,11] that 4-aryl-3-halogenated α,β-unsaturated γ-butyrolactones were prepared from **3** and **4**, we found these methods to be unsatisfactory for practical application. The expensive reagent Ag_2O (3.0 equiv) and highly toxic triphenylarsine (20%) were used to control the regioselectivity when bromide **4** was the starting material, and aryl(tributyl) stannanes were used in NMP at 85 °C for 21−22 h (yield = 55−78%, with side product) when chloride **3** was the starting material. However, under our conditions (25 °C, 48−72 h) 4-aryl-3-chloro-α,β-unsaturated γ-butyrolactone **16** was prepared from **3** and **12** in 91−99% yield. The regioisomer was not observed. The methodology described herein has been successfully applied to the synthesis of Vioxx (**15**, Scheme 3).[16]

Scheme 3. Preparation of Vioxx[a]



[a] Conditions: (a) 2.3 mmol of **3** or **4**, 2.0 equiv of **12**, 5 mol % $PdCl_2(PPh_3)_2$, 2.7 equiv of CsF, 5 mol % $BnEt_3N^+Cl^-$, 1:1 toluene/H_2O, 25 °C; (b) 2.0 equiv of $PhB(OH)_2$, 5 mol % $PdCl_2(PPh_3)_2$, 3.0 equiv of CsF, 5 mol % $BnEt_3N^+Cl^-$, 1:1 toluene/H_2O, reflux; (c) 3.0 equiv of Oxone, wet acetone, 0−25 °C.

In summary, we have developed a simple, efficient, and selective method for preparing bisaryl-γ-butyrolactones and substituted γ-butyrolactones. Mucohalic acids possess a geometrically defined tetrasubstituted olefin and two differentiated vinyl halides and could be used in the synthesis of a variety of biologically active natural products or pharmaceutically important compounds. Further investigations, including extension of the use of these building blocks, will be reported in due course.

Acknowledgment. We thank Dr. Derek Pflum for reviewing this manuscript and providing valuable suggestions.

Supporting Information Available: Experimental procedures, spectral and analytical data for all products, and additional structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Rossi reported preparation of Vioxx in 32% overall yield, starting from **4**, via a Stille-type reaction between tributyl(phenyl)tin and 3-bromo-4-(4-methylthio)phenyl-5*H*-furan-2-one: Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, *12*, 1749.