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Synthesis and Transition Metal-Catalyzed Coupling of a-chloro-b-lactones

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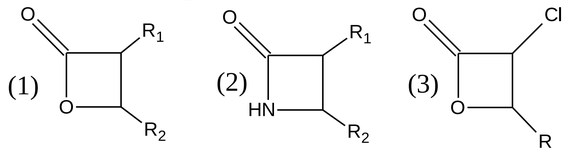
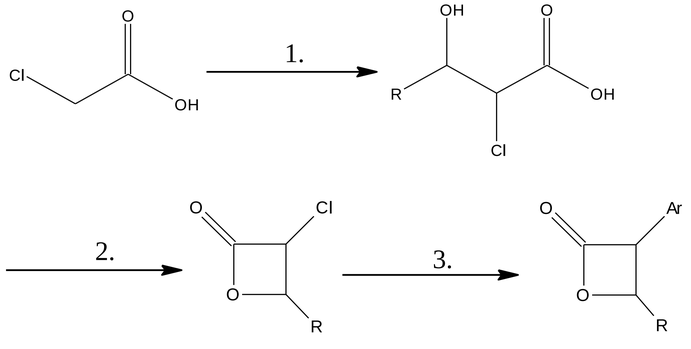
Introduction

β-lactones (1) similar to β-lactams (2), are a class of molecules with a wide range of functions, many of which are still being explored, including as antimicrobials[1] and cholesterol-lowering drugs.[2] Orlistat, for example, is a Food and Drug Administration (FDA)-approved β-lactone drug to treat obesity, as it inhibits fatty acid synthesis and has also been shown to have anti-tumor properties.[3] Many β-lactone derivatives have been synthesized including α-chloro-β-lactone (3),[4] and some have been used in Suzuki Coupling reactions to create other products,[5] though not α-chloro-β-lactone specifically. Developing a novel method for Suzuki Coupling of α-chloro-β-lactones could facilitate synthesis of many α-aryl- and α-alkyl-β-lactones for future medicinal testing.



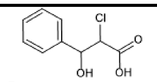
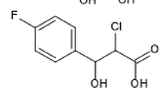
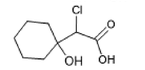
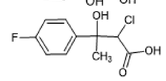
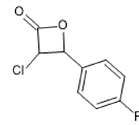
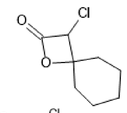
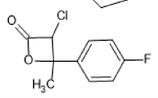
Experimental

1. Aldol synthesis
   a) Chloroacetic acid is reacted with Chx_2BCl and Et_3N at 0°C for 1 hr., followed by ketone/aldehyde addition for 1.5 hrs. and acid-base workup.
2. α-chloro-β-lactone synthesis
   a) The aldol is reacted with DCC or Tosyl Chloride and pyridine at RT for 12 hrs., filtered, and put under rotary vacuum
3. Suzuki Coupling
   a) To α-chloro-β-lactone in THF Pd, PPh_3, K_3PO_4/ K_2CO_3, and boronic acid are added and let stir overnight, followed by acid-base workup.



Results

Table 1. Reaction summaries

Reaction	Reactant	Product	%Yield
Chloroacetic Acid Aldolization	Benzaldehyde		Quantitative
	4-fluorobenzaldehyde		80.9-94.1%
	Cyclohexanone		81.9-94.6%
	4-fluoroacetophenone		96.8%
Fluorophenyl Aldol Lactonization	DCC		79.3%
	Tosyl Chloride, Pyridine		-
Cyclohexyl Aldol Lactonization	Tosyl Chloride, Pyridine		76.8-81.7%
	DCC		90.0%
Fluoroacetophenyl Aldol Lactonization	Tosyl Chloride, Pyridine		77.9%

HNMR analysis (Figure 1) confirmed the successful aldolization of chloroacetic acid in high yields (Table 1) via the described method. FNMR analysis also confirmed the successful lactonization of the aldol, though with an additional peak likely resulting from the breakdown of the lactone into an alkene. The alkene presence was verified from mass spectroscopy of the product which showed a peak of mass 170 g/mol corresponding directly with the respective alkene. Thin-layer chromatography (Figure 2) after catalysis confirmed the successful arylation of the lactone, though at low yields.

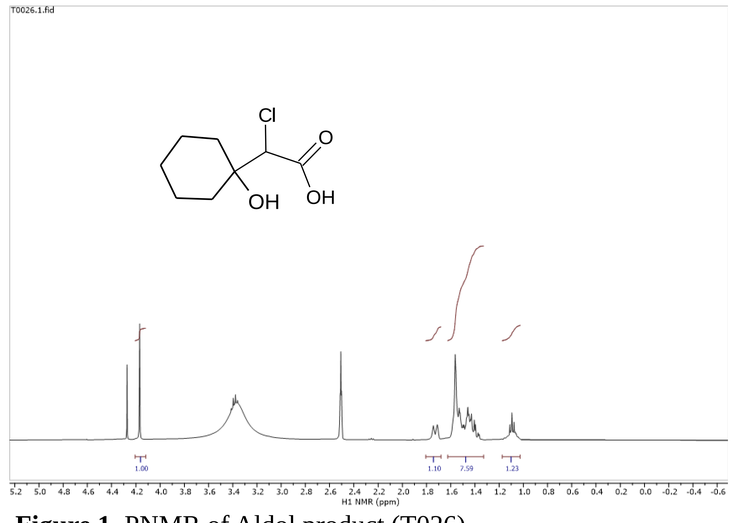


Figure 1. PNMR of Aldol product (T026).

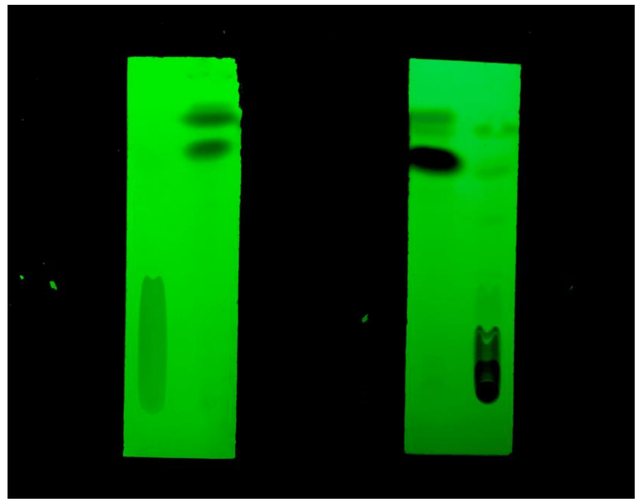


Figure 2. TLC of aldol & α-chloro-β-lactone (left); α-chloro-β-lactone & α-aryl-β-lactone (right)

Conclusion

The three-step aldolization, lactonization, and Suzuki coupling of chloroacetic acid has furnished the resultant α-aryl-β-lactone, though further testing will be required to optimize the methods for maximum yields. Preventing lactone breakdown into the alkene and finding better methods to purify the α-aryl-β-lactone are the next major steps in this process. Additionally, experimenting with more substrates to synthesize a library of α-aryl- and α-alkyl-β-lactones should be considered.

References

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