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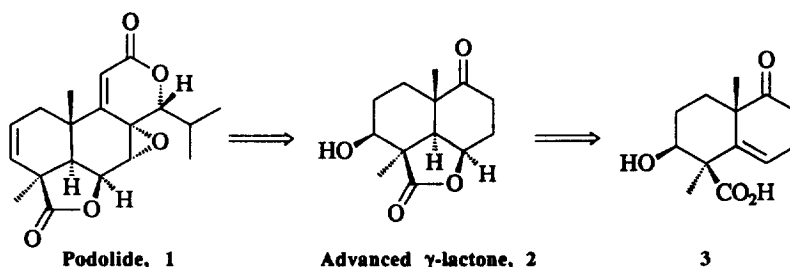
Copper (II) Bromide on Alumina: A New Reagent for Bromolactonization

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Abstract: *Copper (II) bromide supported on alumina has been found to be a new and effective reagent for bromolactonization.*

Our synthesis of the anti-tumor agent, podolide¹ (**1**) and structurally related compounds, as outlined below, was dependent on the formation of a critical intermediate, the advanced γ -lactone (**2**). This γ -lactone was envisioned to arise from a *halo*lactonization of the unsaturated acid (**3**). Unfortunately, this transformation was not trivial as typical lactonization procedures did not yield the desired lactone.



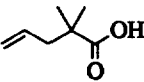
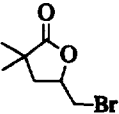
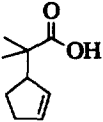
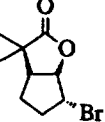
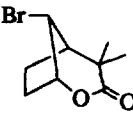

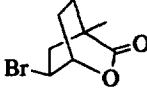
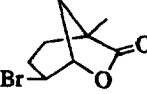
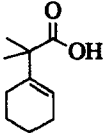
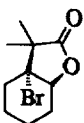
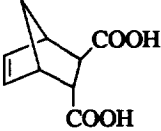
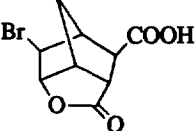
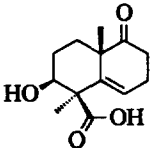
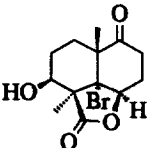
Many methods have been documented for the synthesis of the lactone functionality. Classically, reagents which are a source of electrophilic halogen are utilized. Reagents of choice include: I_2/KI^2 , $Br_2/CHCl_3^3$, or NBS/THF/AcOH.⁴ However, unsaturated acid **3** either failed to cyclize or did so poorly under the aforementioned conditions. Therefore, it became necessary to discover another potential reagent to affect this transformation.

Copper (II) bromide supported on alumina⁵ was recognized as a potential source of electrophilic bromine. It is known that copper (II) bromide, upon heating, thermally decomposes into Br_2 and copper (I) bromide.^{6,7} Kodomari recently used copper (II) bromide for electrophilic substitution reactions of arenes.⁸ We have found that this reagent is useful in synthesis of bromolactones from a variety of unsaturated carboxylic acids.

Typical reaction sequence: A round-bottomed flask was charged with a solution of carboxylic acid (1.2 mmol) in chloroform (100 mL). $CuBr_2$ on Al_2O_3 (6 mmol) was added, the reaction placed in a pre-heated 65°C oil bath and heated 3 to 96 hours. The reaction was cooled, filtered and the remaining copper salts were washed well with methanol. The filtrate was evaporated and the residue partitioned between ether and water. Extraction yielded the desired products. The following table illustrates the utility of copper (II) bromide on alumina as a reagent for bromolactonization.

Application to a variety of simple unsaturated carboxylic acids and the formation of the corresponding bromolactones in moderate to excellent yields, justifies the use of copper (II) bromide supported on alumina as a new reagent for bromolactonization.

Table 1: Bromolactonization of Unsaturated Carboxylic Acids

Substrate	Time	Product(s)	Yield (Ratio)	Lit. Prep.
	96 hrs		98%	NA ^a 85% ^{b,9}
	72 hrs	 	60% (3:1)	NA ^{a,b}
	72 hrs	 	84% (1:2)	ref 10 ^a 96% (0:1) ^{b,11}
	72 hrs		40%	ref 12 ^a NA ^b
	24 hrs		41%	ref 13 ^a 99% ^{b,14}
	3 hrs		47%	21% ^{a,15} 8% ^{b,15}

a. Bromolactone preparation
b. Iodolactone preparation

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