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A PRACTICAL SYNTHESIS OF (+)-BIOTIN THROUGH PALLADIUM HYDROXIDE ON CHARCOAL-CATALYZED FUKUYAMA COUPLING REACTION

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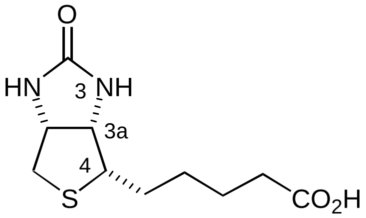
Abstract – The Fukuyama coupling reaction of thiolactone (**2**) with 5-ethoxy-5-oxopentylzinc iodide (**4**) in the presence of 0.65 mol% of non pyrophoric palladium hydroxide on charcoal (Pearlman’s catalyst) provided a vinyl sulfide (**3**) carrying a C-4 side chain of (+)-biotin (**1**) in 87% yield.

(+)-Biotin (**1**) has received considerable attention because of the useful biological properties for human nutrition and animal health.[1] Among a number of synthetic approaches to **1**,[2] a method utilizing thiolactone (**2**) as a key intermediate is considered to be most attractive.[3] We have recently reported a short step synthesis of **1** *via* Fukuyama coupling reaction[4] of **2** with 5-ethoxy-5-oxopentylzinc iodide (**4**).[5] The method, however, requires 5 mol% of pyrophoric palladium on charcoal (Pd/C). From a practical point of view, reducing the amount of the expensive palladium catalyst and eliminating the dangerous operation of adding pyrophoric Pd/C to an organic solvent with a low flash point are highly desirable. Reported herein is an improved method for the installation of the C-4 side chain of **1** through the Fukuyama coupling reaction of **2** with **4** in the presence of non pyrophoric palladium hydroxide on charcoal ($Pd(OH)_2/C$, Pearlman’s catalyst).



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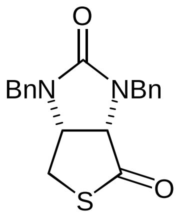

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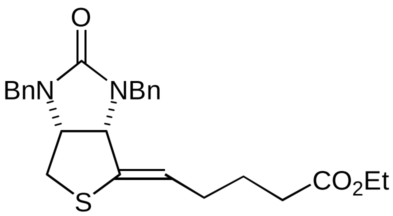

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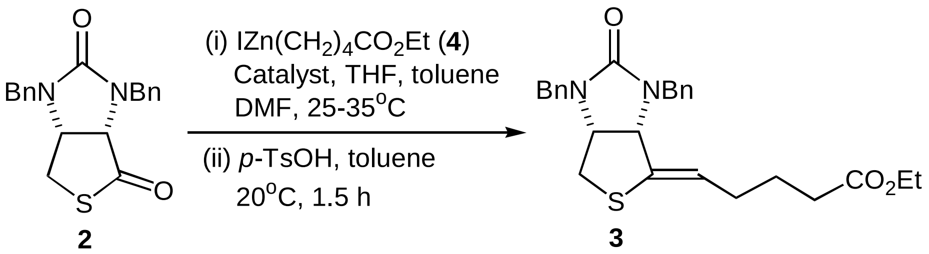
[1] Dedicated to Professor Albert I. Meyers in celebration of his 70th birthday.

The zinc reagent (**4**) was prepared according to a reported procedure[5a] and allowed to react with **2** in the presence of the palladium catalyst of varying amount (Table 1). Use of 5 mol% of Pd/C provided the coupling product (**3**) in 92% yield after dehydration with *p*-toluenesulfonic acid (Entry 1). However, reducing the amount of Pd/C to 2 mol% considerably prolonged the reaction period (1.5 to 17 h) to give **3** in 79% yield (Entry 2). While $Pd(OH)_2/C$ has been used as a highly active catalyst for hydrogenolysis of benzylamines[6] and allylic acetates,[7] and hydrostannation of alkenes with tributyltin hydride,[8] its application to carbon-carbon bond forming reactions has never been reported. The catalyst is non pyrophoric prior to exposure to a reducing agent and "Pd/C" that results *in situ* from reduction of $Pd(OH)_2/C$ may be highly active. We thus tested $Pd(OH)_2/C$ for the coupling reaction of **2** with **4**. As expected, the reaction was remarkably accelerated by the use of $Pd(OH)_2/C$ (2.6 mol%) to complete the reaction in 1 h providing **3** in 90% yield (Entry 3). The high reaction rate and yield were as well observed with such a low catalyst loading as 0.65 mol% (87% yield, Entry 5).[9] To the best of our knowledge, this represents the first example of the use of $Pd(OH)_2/C$ for the carbon-carbon bond forming reactions. The compound (**3**) was converted to (+)-biotin (**1**) in 73% yield according to a reported procedure[5a] *via* hydrogenation followed by removal of the protective groups.

Table 1. The Fukuyama Coupling Reaction of **2** with **4**.[a]



Entry	Catalyst[b]	mol%	Period (h)	Yield (%)[c]
1	Pd/C	5	1.5	92
2	Pd/C	2	17	79
3	$Pd(OH)_2/C$	2.6	1	90
4	$Pd(OH)_2/C$	1.3	2	84
5	$Pd(OH)_2/C$	0.65	2	87
6	$Pd(OH)_2/C$	0.32	3	78

[a] The reactions were conducted on 31 mmol scale. [b] Purchased from Kawaken Fine Chemicals Co., Ltd. [c] Isolated yield.

In conclusion, a highly efficient synthesis of (+)-biotin (**1**) through $Pd(OH)_2/C$-catalyzed Fukuyama coupling reaction of **2** with **4** was accomplished. The high yield, simple operation and low catalyst loading would permit a practical access to (+)-biotin of growing significance. Further application of $Pd(OH)_2$/C to other cross coupling reactions are currently under investigation and will be reported elsewhere in due course.

REFERENCES AND NOTES

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9. **Experimental procedure (Table 1, Entry 5)**: Into a suspension of zinc powder (Merck, < 45 μm) (7.32 g, 110 mmol) in THF (23 mL) was added 1, 2-dibromoethane (250 μL, 2.9 mmol) and the mixture was refluxed for 5 min. After cooling the mixture to 20^{o}C, TMSCl (250 μL, 2 mmoL) was added and the slurry was stirred for 15 min. Ethyl 5-iodopentanoate (24.8 g, 97 mmol) was then added dropwise to the mixture at 30-60^{o}C for 1 h to give a zinc reagent (**4**). Into the mixture containing **4** were added thiolactone (**2**) (10.5 g, 31 mmol), toluene (35 mL), DMF (2.3 mL) and 10% $Pd(OH)_2$ /C (Kawaken Fine Chemicals Co., Ltd.) (218 mg, 0.2 mmol) at 20^{o}C and the mixture was stirred at 25-35^{o}C for 2 h. The mixture was filtered through Celite and the filtrate was washed successively with 1N HCl, sat. aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and evaporated. The residue dissolved in toluene (78 mL) was treated with *p*-toluenesulfonic acid monohydrate (590 mg, 3.1 mmol) and the mixture was stirred at 20^{o}C for 1.5 h. The mixture was washed with water and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:2) to give **3** (12.2 g, 87%).