Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1635–1637
Tetrahedron Letters

A novel procedure for the preparation of zinc reagents: a practical synthesis of (+)-biotin

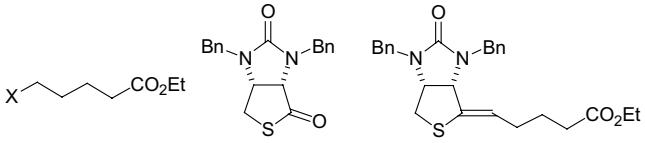
Mayumi Kimura and Masahiko Seki*

Process Chemistry Research Laboratories, Tanabe Seiyaku Co., Ltd, 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan

Received 26 November 2003; revised 17 December 2003; accepted 22 December 2003

Abstract—The use of bromine for activation of zinc dust allowed smooth and reproducible reduction of iodide **1** to the corresponding zinc reagent **2**. The zinc reagent **2** obtained by the present protocol was allowed to the Fukuyama coupling reaction with thiolactone **3** to provide a key intermediate **4** for (+)-biotin in high yield using a reasonably fair amount of **1** (1.4 equiv).

Zinc reagents have received considerable attention due to its tolerance for the presence of various functional groups, safe handling, and low cost.[1] However, to the best of our knowledge, application of the zinc reagents derived from α-non-activated alkyl iodides to the industrial production has never been reported possibly because of poor reproducibility in the preparation of the zinc reagents. The method for activation of zinc dust is the most significant issue for the preparation of the zinc reagents and a number of approaches such as those employed TMSCl,[2] 1,2-dibromoethane,[3] and iodine[4] have hitherto been devised. Among them, the most popular method is the Knochel's procedure[5] involving the treatment of zinc dust with TMSCl followed by 1,2-dibromoethane. It is, however, not entirely satisfactory for a practical use because of recently found carcinogenic toxicity of 1,2-dibromoethane. In a course of our synthetic studies of (+)-biotin,[6] coupling reaction of thiolactone **3** with zinc reagent **2** was investigated.[6a–d] While, in the optimal procedure,[6d] we employed TMSCl[2] for activating zinc dust, it, however, suffered from poor reproducibility and required excess iodide **1** (2.5 equiv) for attaining the complete conversion of the coupling reaction (see, Table 1, entry 1). Disclosed herein are highly efficient, safe, and reproducible method for the preparation of the zinc reagent **2** by the use of inexpensive bromine and its application to the Fukuyama coupling reaction[6a–d,7] with **3** to **4** without requiring the excess iodide **1**.



1: X = I
2: X = ZnI
3
4

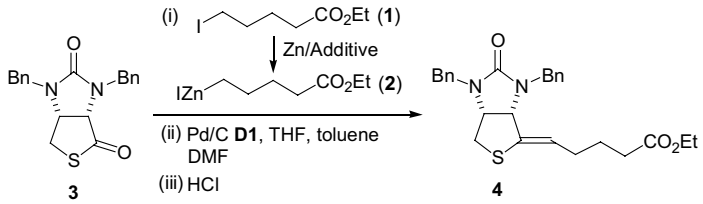
The preparation of zinc reagent **2** and the Fukuyama coupling reaction with **3** were investigated by employing various activating reagents for zinc dust (Table 1). In our previously reported activation of zinc dust with TMSCl,[2,6d] the yield of the coupling product **4** dramatically decreased from 95% to 59% by reducing the amount of iodide **1** from 2.5 to 1.4 equiv (Table 1, entries 1 and 2). As the Fukuyama coupling reaction has been reported not to proceed with dialkylzinc (R_2Zn),[7] the Schlenk equilibrium[1a] of the zinc reagents should lie to the left to achieve the maximum utilization of the reduced iodide (Scheme 1). We envisioned that addition of zinc(II) salt (ZnX_2) may shift the equilibrium toward the desired RZnX, whereby the amount of the required iodide **1** should be decreased.

To this end, we initially employed zinc iodide as an additive for the Fukuyama coupling reaction. Zinc iodide was smoothly generated by the reaction of zinc dust with iodine.[4] However, subsequent reduction of **1** to the corresponding zinc reagent **2** lacks for reproducibility: the reaction sometimes stopped without completion. Nonetheless, as we expected, the zinc reagent **2** obtained was treated with thiolactone **3** in the presence of Pd/C **D1**[8] (10 wt%, 0.64 mol%) to provide the

* Corresponding author. Tel.: +81-663002456; fax: +81-663002816; e-mail: m-seki@tanabe.co.jp

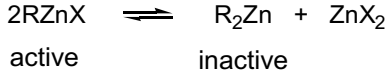
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.119

Table 1. The Fukuyama coupling reaction of thiolactone **3** with zinc reagent **2** through the activation of zinc dust with various additives



Entry	Additive (equiv)[a]	Iodide (**1**)[b]	Assay yield (%)[c]
1	TMSCl (0.1)	2.5	95
2	TMSCl (0.1)	1.4	59
3	I_2 (0.25)	1.4	88
4	1,2-Dibromoethane (0.5)	1.4	84
5	Br_2 (0.5)	1.4	94 (94)[d]

[a] Equivalent to **1**.
[b] Equivalent relative to **3**.
[c] Determined by HPLC.
[d] Isolated yield.



Scheme 1. The Schlenk equilibrium of zinc reagents and the utility for the Fukuyama coupling reaction.

coupling product **4** in 88% yield without need for excess iodide **1** (Table 1, entry 3).

To ensure the reproducibility in the reduction of **1** to **2**, the addition of $ZnBr_2$ in place of ZnI_2 was then examined. In our initial study, the anhydrous zinc bromide was generated by the treatment of zinc dust with 1,2-dibromoethane under reflux with simultaneous activation of zinc dust. In accord with our expectation, a smooth and reproducible formation of **2** was achieved by the addition of **1** to the suspension involving activated zinc dust and zinc bromide. The Fukuyama coupling reaction of the resulting **2** with **3** smoothly proceeded to provide **4** in 84% yield (Table 1, entry 4).

To eliminate a risk for handling carcinogenic 1,2-dibromoethane, the use of bromine was examined. Rapid discoloration of bromine, that is, formation of zinc bromide, was observed when bromine was added into the suspension of zinc dust. Gratifyingly, when the suspension was treated with iodide **1**, a highly reproducible formation of zinc reagent **2** was accomplished. The zinc reagent **2** obtained was subjected to the Fukuyama coupling reaction with **3** to provide the desired coupling product **4** in 94% yield by the use of 1.4 equiv of **1** (Table 1, entry 5).[9] Although the precise roles of zinc bromide in the formation of **2** and in the Fukuyama coupling reaction with **3** are not clear at the present time, the use of bromine permits highly cost efficient and reproducible preparation of **2** and the subsequent successful Fukuyama coupling reaction with **3**.

In conclusion, a facile and economical synthesis of zinc reagent **2** with bromine used as a novel activator was accomplished. The protocol allowed decrease of expensive iodide **1** from 2.5 to 1.4 equiv in the Fukuyama coupling reaction with thiolactone **3** as well. The method is so practical that it has already been applied to a large-scale preparation employing more than 500 kg of thiolactone **3** in a 5000 L reactor. The use of inexpensive reagent, easy operation, reproducibility and high yield of the present protocol would permit the most practical access to the zinc reagents that are effective for the Fukuyama coupling reaction. Since ethanethiol esters obtained from a variety of aliphatic and aromatic carboxylic acids show higher activities in the Fukuyama coupling reaction than cyclic thiol esters such as thiolactone **3**,[6b] the present protocol should find wide application to the synthesis of functionalized ketones other than the (+)-biotin intermediate **4**. Elucidation of the reaction mechanism and the scope and limitation in the preparation of other types of zinc reagents and the Fukuyama coupling reaction therewith, is currently under investigation, which will be reported elsewhere in due course.

Acknowledgements

The authors wish to thank Degussa Japan Co., Ltd. for disclosing the chemical properties of Pd/C **D1**.

References and notes

1. (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117; (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC LLC: New York, 1996; (c) Knochel, P.; Jones, P. *Organozinc Reagents A Practical Approach*; Oxford University Press: New York, 1999; (d) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.

2. (a) Gawronsky, J. K. *Tetrahedron Lett.* **1984**, *25*, 2605; (b) Picotin, G.; Miginiac, P. *Tetrahedron Lett.* **1987**, *28*, 4551; (c) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796.
3. (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475; (b) Bellasoued, M.; Gaudemar, M.; El Borgi, A.; Baccar, B. *J. Organomet. Chem.* **1985**, *280*, 165; (c) Knochel, P.; Normant, J. F. *J. Organomet. Chem.* **1986**, *309*, 1; (d) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 4495; (e) Gaudemar, M. *Organomet. Synth.* **1988**, *4*, 416; (f) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789; (g) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390; (h) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366; (i) Berk, S. C.; Yeh, M. C. P.; Jeang, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053; (j) Achyutha Rao, S.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735; (k) Yeh, M. C. P.; Chen, H. G.; Knochel, P. *Org. Synth.* **1992**, *70*, 195.
4. (a) Newman, M. S. *J. Am. Chem. Soc.* **1942**, *64*, 2131; (b) Palmer, M. H.; Reid, J. A. *J. Chem. Soc.* **1960**, 931; (c) Huo, S. *Org. Lett.* **2003**, *5*, 423.
5. Knochel, P.; Yeh, M. C. P.; Beck, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
6. (a) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099; (b) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, *42*, 429; (c) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039; (d) Mori, Y.; Seki, M. *Heterocycles* **2002**, *58*, 125; (e) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571; (f) Seki, M.; Hatsuda, M.; Mori, Y.; Yamada, S. *Tetrahedron Lett.* **2002**, *43*, 3269; (g) Seki, M.; Mori, Y.; Hatsuda, M.; Yamada, S. *J. Org. Chem.* **2002**, *67*, 5527; (h) Seki, M.; Shimizu, T.; Inubushi, K. *Synthesis* **2002**, 361; (i) Mori, Y.; Kimura, M.; Seki, M. *Synthesis* **2003**, 2311; (j) Seki, M.; Kimura, M.; Hatsuda, M.; Mori, Y.; Yamada, S. *Tetrahedron Lett.* **2003**, *44*, 8905.
7. Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.
8. Purchased from Degussa Japan Co., Ltd. Catalysts Division. The chemical properties of Pd/C **D1** are as follows: Impregnation degree = 50–150 nm; reduction degree = 0–25%; Pd dispersion = 29%; water content = ca. 3%.
9. A typical procedure for the preparation of zinc reagents using bromine and the Fukuyama coupling reaction, preparation of **4**: To a solution of zinc dust (9.3 g, 0.14 mol) in THF (18 mL) and toluene (12 mL) was added bromine (5.8 g, 36 mmol) at 10–40 °C for 15 min and the mixture was heated up to 50 °C. To the mixture was added dropwise at 50–60 °C a solution of ethyl 5-iodopentanoate **1** (18.6 g, 72.8 mmol) over a period of 1 h. After stirring the mixture at the same temperature for 1 h, the mixture was cooled down to 30 °C. To the mixture was added toluene (36 mL), thiolactone **3** (17.6 g, 52.0 mmol) and 10% Pd/C **D1**[8] (0.5 g, 0.45 mmol) in DMF (4.4 mL). After stirring the mixture at 28–40 °C for 5 h, 18 wt% HCl (34 mL) was added to the mixture at 10–30 °C. After stirring the mixture at 20 °C for 1 h, the mixture was filtered. The organic layer of the filtrate was separated and washed successively with water (three times), sat. aq. sodium sulfite and water. The extracts were combined and evaporated to give **4** [22.0 g, 94% (assay yield, determined by HPLC: L-Column ODS (Daicel), $CH_3CN/H_2O = 65:35$, 1.0 mL/min, 40 °C, 254 nm)], which was pure enough to be used for the next step, that is, hydrogenation of the double bond.[6a] Purification of the residue by silica gel column chromatography (hexane/AcOEt = 5:2) provided pure sample of **4** (22.0 g, 94%) as a viscous oil. $[\alpha]_D^{25}$ +190.9° (*c*, 0.95, MeOH); IR (KBr) ν 2932, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95–7.08 (m, 10H), 5.13 (dd, $J = 8.0$ Hz, 1H), 4.59 (m, 2H), 3.72–3.99 (m, 6H), 2.62–2.71 (m, 2H), 1.95–1.99 (m, 2H), 1.72–1.88 (m, 2H), 1.35–1.45 (m, 2H), 0.96 (dd, $J = 8.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.1, 137.9, 159.0, 173.3 (4s), 59.0, 64.6, 125.7, 127.3–129.0 (13d), 24.2, 31.1, 33.6, 37.1, 44.9, 46.5, 60.3 (7t), 14.3 (q); HRMS m/z $(M-1)^-$: Calcd for $C_{26}H_{30}N_2O_3S$, 450.1977. Found, 450.1966.