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Tetrahedron Letters 45 (2004) 7343–7345

Tetrahedron Letters

A novel procedure for the synthesis of multifunctional ketones through the Fukuyama coupling reaction employing dialkylzincs

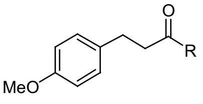
Yoshikazu Mori[a] and Masahiko Seki[b,*]

[a]*Process Chemistry Research Laboratories, Tanabe Seiyaku Co., Ltd, 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan*
[b]*Export and Import Group, Purchasing Department, Logistics Division, Tanabe Seiyaku Co., Ltd, 3-2-10, Dosho-Machi, Chuo-Ku, Osaka 541-8505, Japan*

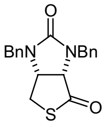
Received 1 July 2004; revised 29 July 2004; accepted 30 July 2004

Abstract—Treatment of thiol esters **1** with dialkylzincs **2** in the presence of zinc bromide, that was in situ prepared from zinc dust and bromine, provided various functionalized ketones **3** in high yields. The reaction mechanism, which may shift the Schlenk equilibrium from dialkylzincs **2** to reactive alkylzinc bromide **5**, was postulated to account for the facile coupling reaction.

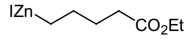
Multifunctional ketones have received considerable attention due to the significance in the preparation of drugs and natural products. Development of their efficient synthetic method has thus been a subject of ongoing interest.[1] We have reported a practical synthesis of the ketones through heterogeneous Pd/C-catalyzed Fukuyama coupling reaction[2] of thiol esters with alkylzinc iodides (RZnI).[3] The use of dialkylzincs (R_2Zn) for the reactant can be an attractive alternative because of the stability over the corresponding RZnX. However, Fukuyama and co-workers have reported an unsuccessful coupling reaction of thiol ester **1a** with Et_2Zn **2a** in the presence of homogeneous Pd catalyst, $PdCl_2(PPh_3)_2$.[2] They unexpectedly got a reduction product, that is, aldehyde **4**, instead of the desired ketone **3a**. We have recently reported an improved Fukuyama coupling reaction of thiolactone **1b** with alkylzinc iodide **5a** in the presence of $ZnBr_2$ and heterogeneous Pd/C, and have postulated a mechanism involving a shift of the Schlenk equilibrium from inactive R_2Zn **2** to the active RZnX **5** (X = Br) species by the addition of ZnX_2 (X = Br) (Scheme 1).[3d] If the hypothesis is true, the Fukuyama coupling reaction employing R_2Zn **2** would take place in the presence of $ZnBr_2$. Reported herein are the successful results of the Fukuyama coupling reaction of R_2Zn **2** with thiol esters in the presence of $ZnBr_2$.



1a: R = SEt
3a: R = Et
4: R = H

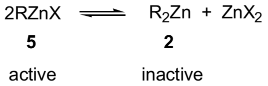


1b



5a

In our initial study, the reaction of Et_2Zn with thiol ester **1a** was tested under various conditions. Treatment of **1a** with Et_2Zn **2a**[4] in the presence of Pd/C[5] in a mixed solvent of THF and toluene provided the desired ketone **3a** albeit in a poor yield (36%, Table 1, entry 1). To improve the yield, addition of $ZnBr_2$ to the reaction mixture was examined. Into a mixture of $ZnBr_2$ (1.0 equiv), freshly prepared from zinc dust (2.0 equiv) and bromine (1.0 equiv) in THF and toluene, were added thiol ester **1a** and Pd/C followed by Et_2Zn **2a**. After an initial exothermic reaction and stirring at 20 °C for 17 h, the desired ketone **3a** was obtained expectedly in a much higher yield (84%) (Table 1, entry 2). Addition of DMF[3a] was effective for the coupling



$$\underset{\substack{\mathbf{5}\\ \text{active}}}{2RZnX} \rightleftharpoons \underset{\substack{\mathbf{2}\\ \text{inactive}}}{R_2Zn} + ZnX_2$$

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

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[*] Corresponding author. Tel.: +81 6 6205 5498; fax: +81 6 6205 5178; e-mail: m-seki@tanabe.co.jp

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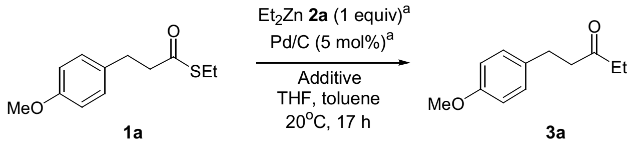
doi:10.1016/j.tetlet.2004.07.148

Table 1. The Fukuyama coupling reaction of thiol ester **1a** with Et_2Zn **2a**



Entry	Additive (equiv)[b]	Yield (%)[c]
1	—	36
2	$ZnBr_2$ [Zn (2.0)/Br_2 (1.0)]	84
3	$ZnBr_2$ [Zn (2.0)/Br_2 (1.0)], DMF (4.9)	95

[a] Equivalent relative to thiol ester **1a**.

[b] Equivalent relative to Et_2Zn **2a**.

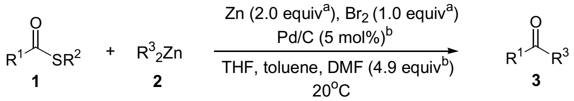
[c] Isolated yield.

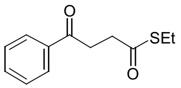
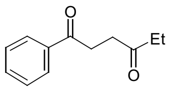
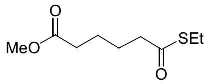
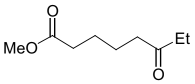
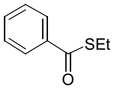
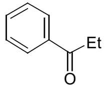
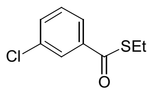
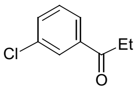
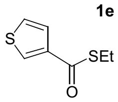
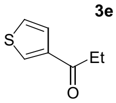
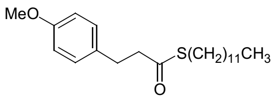
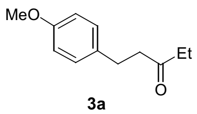
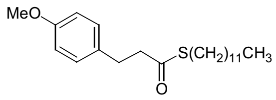
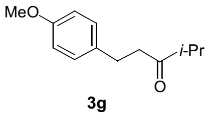
reaction: a complete conversion of the reaction was accomplished by the addition of 4.9 equiv of DMF to the reaction mixture, providing **3a** in an excellent yield (95%) (Table 1, entry 3).[6]

The present method was applied to the coupling reaction of various substrates (Table 2). Thiol esters **1b**,**c** and **1e** carrying a ketone, an ester and Cl group were applicable to the coupling reaction to afford the corresponding ethyl ketones **3b**,**c** and **3e** in high yields (Table 2, entries 1, 2 and 4). Aromatic thiol esters **1d**, **1e** and **1f** were less reactive than aliphatic counterparts **1a**,**b** and **1c**: longer reaction periods were required to obtain a sufficient conversion (compare Table 1, entry 3 and Table 2, entries 1–2 with Table 2, entries 3–5). An odorless thiol ester **1g**,[7] prepared from dodecane thiol, gave the desired ethyl ketone **3a** in good yield as well (Table 2, entry 6). The use of sterically more hindered diisopropylzinc **2b** furnished isopropyl ketone **3g** albeit in a moderate yield (Table 2, entry 7).

In conclusion, a novel and efficient synthesis of functionalized ketones through a coupling reaction of dialkylzincs with thiol esters was worked out. Although preparation of the ketones employing dialkylzincs in the presence of homogeneous Pd or Cu catalyst has been

Table 2. The Fukuyama coupling reaction employing R_2Zn



Entry	Thiol ester **1**	R_2Zn **2** (1 equiv[b])	Ketone **3**[c]	Period (h)	Yield (%)[d]
1	 **1b**	Et_2Zn **2a**	 **3b**	17	95
2	 **1c**	Et_2Zn **2a**	 **3c**	17	Quant.
3	 **1d**	Et_2Zn **2a**	 **3d**	48	85
4	 **1e**	Et_2Zn **2a**	 **3e**	48	83
5	 **1f**	Et_2Zn **2a**	 **3f**	48	57
6	 **1g**	Et_2Zn **2a**	 **3a**	48	72
7	 **1g**	*i*-Pr_2Zn[e] **2b**	 **3g**	48	56

[a] Equivalent relative to R_2Zn **2**.

[b] Equivalent relative to thiol ester **1**.

[c] All new compounds were fully characterized by IR, NMR and MS spectra.

[d] Isolated yield.

[e] 2.0 M toluene solution of *i*-Pr_2Zn was employed for the reaction.

reported, they require unstable and corrosive acid chloride as the substrates.[8] The present method can be an attractive alternative to these methods. While, at the present time, the dialkylzincs employed are limited to simple commercially available one, that is, Et_2Zn and $i\text{-}Pr_2Zn$, it should find a wide application to a practical synthesis of functionalized ketones, when combined with the recently developed versatile synthesis of dialkyl and diarylzincs.[9]

Acknowledgements

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

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4. 1.1 M toluene solution of Et_2Zn (Aldrich) was employed for the coupling reaction.
5. The Pd/C catalyst employed in this study was purchased from Degussa Japan Co., Ltd and has the following chemical properties: impregnation depth, 200–500 nm (thick shell); reduction degree, 0–25%; Pd dispersion, 35%; water content, less than 3 wt%. The catalyst is commercially available at Degussa Japan Co., Ltd.
6. *A typical procedure for the Fukuyama coupling reaction employing dialkylzinc, synthesis of ethyl ketone* **3a** *from thiol ester* **1a**: Into a suspension of zinc dust (584 mg, 8.93 mmol) in THF (2.5 mL) and toluene (2.5 mL) was added dropwise bromine (0.23 mL, 4.46 mmol) at <30 °C. Thiol ester **1a** (1.00 g, 4.46 mmol) in toluene (1 mL) was then added to the mixture at 20 °C followed by Pd/C[5] (20 wt%, 123 mg, 0.23 mmol). Into the mixture was added dropwise Et_2Zn (1.1 M toluene solution, Aldrich, 4.05 mL, 4.46 mmol) at <25 °C followed by DMF (1.7 mL). The mixture was stirred at 20 °C for 17 h. Into the suspension was carefully added 18% aq HCl (10 mL) at <30 °C to dissolve excess zinc dust. The mixture was filtered and the filtrate was separated. The resulting organic phase was washed three times with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (hexane to hexane/AcOEt = 30:1) to afford ethyl ketone **3a** (814 mg, 95%) as a yellow oil. IR (ATR) $\nu = 1712\,cm^{-1}$; ^1H NMR ($CDCl_3$) δ 7.10 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 3.78 (s, 3H), 2.87–2.82 (m, 2H), 2.72–2.67 (t, $J = 7.6$ Hz, 2H), 2.39 (q, $J = 7.3$ Hz, 2H), 1.04 (t, $J = 7.3$ Hz, 3H); EI *m/z* 192 (M^+).
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