

Novel Zn/ZnI₂-promoted cross-coupling of acrylic acid esters with arylaldehydes to α -aroaladipic acid esters†

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Received (in Cambridge, UK) 3rd September 2002, Accepted 6th November 2002

First published as an Advance Article on the web 20th November 2002

Cross-coupling of alkyl acrylates and arylaldehydes was achieved by treatment with metallic zinc and zinc(II) iodide in DMF, giving dialkyl α -aroaladipates in moderate yields.

Reductive coupling of carbonyl compounds (pinacol coupling)¹ or α,β -unsaturated carbonyl/carboxyl compounds² is one of the important methods for the construction of a highly functionalized framework. Cross-coupling of carbonyl compounds with α,β -unsaturated esters can also be achieved by SmI₂, giving the γ -hydroxy esters or γ -lactones with good stereoselectivity.³

Metallic zinc is widely utilized as a relatively mild reducing reagent and addition of an activator such as acids or Lewis acids is required to enhance the reactivity.⁴ Another role of zinc is based on a reductant towards a co-existing metallic salt, generating the reactive low-valent metal species. For example, recent reports from our laboratory have demonstrated a catalytic pinacol coupling reaction promoted by the combination of a catalytic amount of vanadium or titanium salt with metallic zinc in the presence of a silylating or acylating reagent.⁵ In this paper we report that Zn/ZnI₂ promotes the novel 2:1 coupling of an acrylic acid ester and an aromatic aldehyde to give the corresponding α -aroaladipate.

When methyl acrylate (1 mmol) and benzaldehyde (2 mmol) were treated with metallic zinc (4 mmol) and zinc(II) iodide (1 mmol) in DMF at 70 °C for 24 h, dimethyl α -benzoyladipate (**1a**) was obtained in 50% yield, accompanied by the benzyl alcohol and the pinacol coupling derivative in 19% and 11% yields, respectively (Scheme 1).

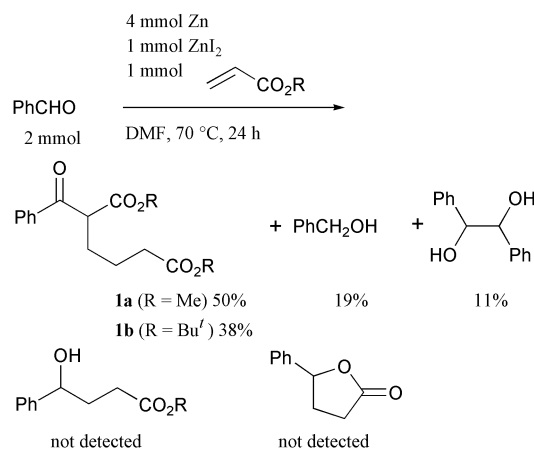
It is noteworthy that **1a** was not produced in the absence of Zn(II) salt. γ -Hydroxy ester, γ -lactone and other reductive cross-coupling products were not detected in the reaction mixture. Other Zn(II) salts such as Zn(OAc)₂ or ZnCl₂ also promoted the reaction, but ZnI₂ was found to be more effective. The reaction did not take place using a less polar solvent such as THF or a protic solvent such as MeOH. Among the non-protic polar

solvent such as DMA, DMI or NMP, DMF gave the best result.

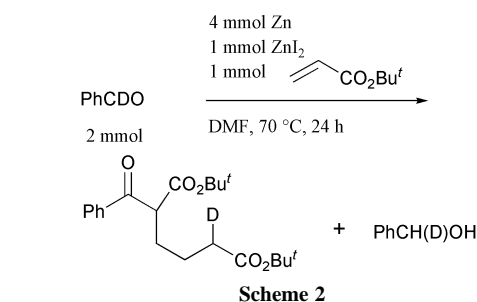
The benzoyl group at the α -position seems to be derived by aldol-type reaction, followed by oxidation of the thus-generated alcoholic intermediate. When PhCDO was treated with Zn/ZnI₂ in the presence of *tert*-butyl acrylate under the similar conditions, the deuterium was selectively introduced into the δ -position of **1b**. A reaction path *via* intermolecular Oppenauer oxidation between the alcoholic intermediate and benzaldehyde might be excluded because only one D was detected in the co-produced benzyl alcohol (Scheme 2).

The reaction was found to be affected by the substituent on aldehydes (Scheme 3).⁶ The yields of **1** in the reaction of *tert*-butyl acrylate with *p*-methyl- (weakly electron-donating group) and *p*-chloro- (weakly electron-withdrawing group) benzaldehyde were 36% and 38%, respectively, which are almost the same as that with benzaldehyde (38%). On the other hand, the reaction did not take place with the aldehydes bearing a strongly donating group such as *p*-methoxybenzaldehyde. As for the aldehydes with a strong electron-withdrawing group such as *p*-trifluoromethylbenzaldehyde, **1g** was not obtained with the quantitative formation of the pinacol coupling product.

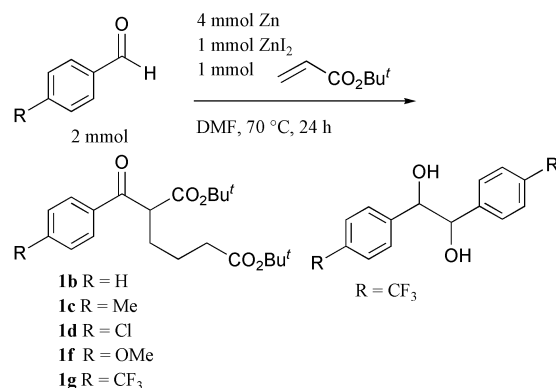
No reductive coupling of methyl acrylate proceeded in the absence of an aldehyde, indicating that the aldehyde might be indispensable for the reductive process. As a possible explanation, a complex generated from Zn, ZnI₂, and an aldehyde might be involved to promote the reductive 1,4-coupling (Scheme 4). The thus-formed zinc dienolate **A** reacts with the aldehyde to afford the zinc chelate **C**. Another pathway to **C** depends on the



Scheme 1

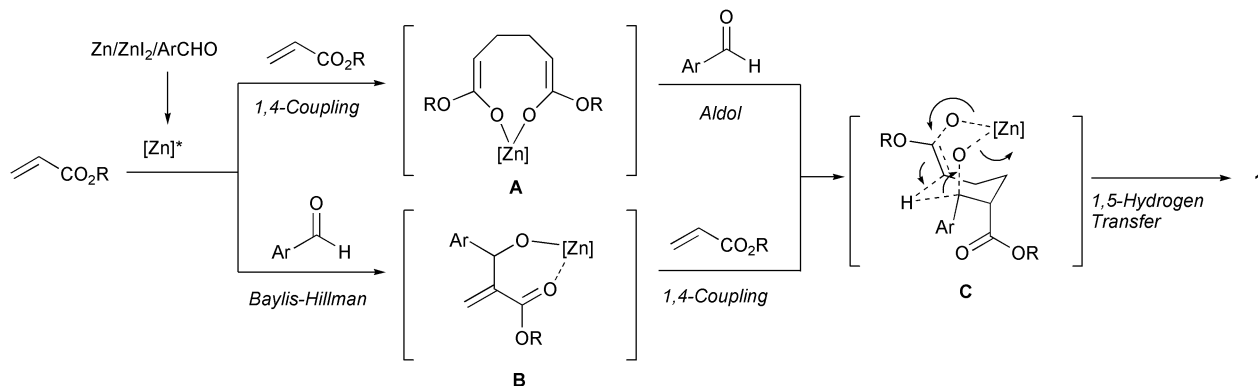


Scheme 2

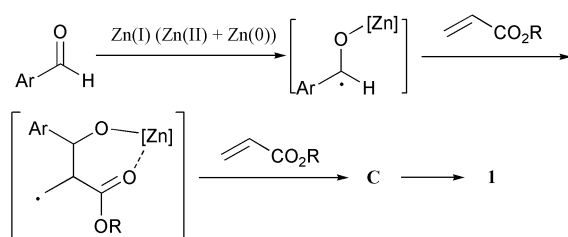


Scheme 3

† Electronic supplementary information (ESI) available: typical experimental procedure and characterization data. See <http://www.rsc.org/suppldata/cc/b208608e/>



Scheme 4



Scheme 5

Lewis-acid promoted Baylis–Hillman reaction⁷ to generate **B**, followed by the reductive 1,4-coupling with the acrylate.⁸ From the zinc chelate **C**, 1,5-hydrogen transfer takes place to give **1**, which is supported by the result with PhCDO as shown in Scheme 2. The 1,5-hydrogen shift could be similar to Tishchenko reaction.⁹ In the present reaction, however, the zinc species appears to affect a redox process. If the proton or hydride shift takes place, the chelated Zn^{2+} would be reduced to Zn^0 . Zn^+ would be generated in the radical process. In both cases, the combination of Zn/ZnI_2 is assumed to play an important role to promote such a process.

As described above, Zn/ZnI_2 promoted the 2:1 cross-coupling reaction of acrylic acid ester and aromatic aldehyde to give the α -aroyladipic acid ester. Combination of Zn , Zn(II) salt and aromatic aldehyde appears to be essential to promote the reaction effectively. Further investigations including the mechanistic study and scope of the reaction are in progress.

The use of the facilities of the Analytical Center, Faculty of Engineering, Osaka University is acknowledged. H. S. thanks the Fujisawa Foundation for financial support.

Notes and references

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- A typical procedure: a 30 mL two-necked round-bottomed flask was charged with 260 mg (4 mmol) of zinc powder, flame-dried, and then purged with argon. A DMF (4 mL) solution of ZnI_2 (319 mg, 1 mmol) and methyl acrylate (90 μL , 1 mmol) was added via syringe. After the mixture was heated at 70 °C, benzaldehyde (212 mg, 2 mmol) was added to the mixture, which was stirred at 70 °C for 24 h. After cooling down to room temperature, the mixture was diluted with ether (10 mL) and then 1.5 M HCl solution (10 mL) was added. After stirring for 10 min, the mixture was filtered through Celite and the aqueous phase extracted with ether (20 mL \times 3). The combined organic phase was washed with H_2O then brine, dried over MgSO_4 , and evaporated *in vacuo*. Purification by silica-gel column chromatography gave the pure product **1a** as a colorless oil (139 mg, 50% yield). **1a**: ^1H NMR (400 MHz, CDCl_3) δ 1.92–2.13 (2H, m), 2.46 (2H, t, $J = 7.0$ Hz), 3.04–3.17 (2H, m), 3.50–3.56 (1H, m), 3.71 (3H, s), 3.74 (3H, s), 7.44 (2H, t, $J = 8.5$ Hz), 7.52 (1H, t, $J = 8.5$ Hz), 7.94 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 27.1 (CH_2), 31.8 (CH_2), 39.7 (CH), 40.5 (CH_2), 51.8 (OCH_3), 52.0 (OCH_3), 128.0 (CH), 128.5 (CH), 133.2 (CH), 136.4 (C), 173.0 (C=O, ester), 175.0 (C=O, ester), 197.4 (C=O, ketone) ppm. IR (neat) 2920, 1735, 1685, 1444, 1371, 1218, 1169 cm^{-1} . Anal. Found: C, 64.68; H, 6.55%. Calc. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.74; H, 6.53%.
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- An alternative mechanism involving a one-electron reduction process is also possible. Zn(I) species, generated from Zn(0) and Zn(II) reacts with arylaldehyde to give a benzyl radical, which adds to the α -position of the acrylate. The chelate radical intermediate then reacts with another acrylate via 1,4-addition to generate **C** (Scheme 5). The authors acknowledge the suggestion of a referee.
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