The Synthesis of 1,4-Diketones via a One-pot Five-component Connecting Reaction Based on Two Acylations of Organozincs Promoted by the Catalysis of a Pd(0) Species

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Unsymmetrical 1,4-diketones were produced via a one-pot five-component connecting reaction based on two kinds of Pd(0)-catalyzed acylations of organozincs using acryloyl chloride and TMSCl in an atmosphere of carbon monoxide.

1,4-Diketones are useful synthetic precursors of heterocyclic compounds[1] and biologically active cyclopentenones.[2] Many methods for preparation of 1,4-diketones by a conjugate addition of acyl anions or their equivalents to α,β-enones[3] or of alkyl radicals in the presence of carbon monoxide have been reported.[4] Recently, we have also developed a practical method for the synthesis of such dicarbonyl compounds via a palladium-catalyzed carbonylative 1,4-addition of organozinc halides to α,β-enones under CO gas (Figure 1).[5]

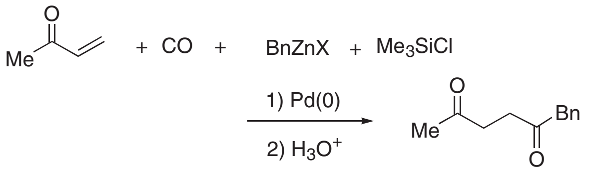


Figure 1. Four-component connecting reaction leading to 1,4-diketones.[5]

Vinyl ketones and acrolein are good Michael acceptors.[6] However, only a few vinylic ketones are commercially available and they are expensive, and most of them are labile due to polymerization.[7] We have been interested in the in situ catalytic generation of such vinylic ketones to be used in our palladium-catalyzed carbonylative 1,4-addition of organozinc halides under CO gas.[5]

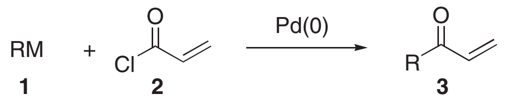


Figure 2. Preparation of vinyl ketones by Pd(0)-catalyzed cross-coupling reaction.[8–11]

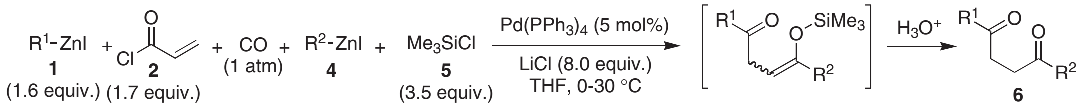
Stille (1979) reported that a palladium-catalyzed cross-coupling reaction of acid chlorides and organotins produced the corresponding ketones, including methyl vinyl ketone from acryloyl chloride or benzalacetone from cinnamoyl chloride, in good yields (Figure 2).[8] Negishi and co-workers (1983)[9] reported a similar catalytic coupling using organozinc chlorides **1**, in which a Pd(0)-catalyst was generated in situ from $PdCl_2(PPh_3)_2$. Before this, Fujisawa (1981)[10] had reported a Pd-catalyzed cross-coupling reaction of acid chlorides and benzylzinc bromides being prepared in situ from benzyl bromide with $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ and zinc powder. Yoshida (1985)[11] reported a similar catalytic cross-coupling using $Pd(PPh_3)_4$ via an in situ preparation of organozinc iodides from alkyl iodides and Zn–Cu couple. These reports encouraged us to make one palladium catalyst catalyze two reactions in order to devise a one-pot five-component connecting reaction for preparation of 1,4-dicarbonyl compounds: a catalyst, $Pd(PPh_3)_4$, used for preparation of vinyl ketones, is reused in the four-component connecting reaction.

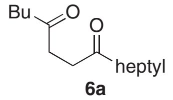
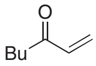
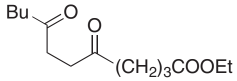
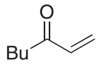
A typical experimental procedure is as follows. To a stirred mixture of LiCl[12] (848 mg, 20 mmol) and $Pd(Ph_3P)_4$ (144 mg, 0.125 mmol) in THF (4 mL) at 0 °C under Ar was added organozinc iodide **1** (THF solution, 4.0 mmol) and then acryloyl chloride **2** (0.34 mL, 4.2 mmol) dropwise. After the mixture had been stirred at room temperature for 4 h, CO gas (1 atm) was introduced using a toy balloon and Me_3SiCl (1.10 mL, 8.75 mmol) was added. To the vigorously stirred mixture was added another organozinc iodide (**4**, THF solution, 2.2 mmol) dropwise over a period of 30 min at 30 °C. After 5 min, the reaction was quenched with a 2 N HCl solution (4 mL), diluted with water (15 mL), and extracted with Et_2O (20 mL × 2). The combined organic layers were washed with water (15 mL) and brine (15 mL) and then dried over $MgSO_4$. The extract was concentrated, and the residue was subjected to column chromatography on silica gel eluted with 5–10:1 hexane/ethyl acetate to afford diketone **6**.

The results are shown in Table 1. When *n*-butylzinc iodide and *n*-heptylzinc iodide were used for **1** and **4**, respectively, the desired pentadecane-5,8-dione **6a** was obtained in 69% isolated yield (89% yield by GC analysis) (Entry 1). No by-product due to cross-coupling of butyl vinyl ketone (**3**) and butylzinc iodide (**1**) was formed. These results are comparable with that of the reaction based on the four-component connecting reaction starting with vinyl ketones (Entry 2) reported recently by us.[5] Another carbonylative 1,4-addition using an organozinc iodide having an ester group to **3** afforded a similar good result (79% yield of **6b**) (Entry 4). In contrast, as shown in Entry 3, the five-component connecting reaction using the same organozinc halide for **4** afforded **6b** in 37% yield (Entry 3). Probably, $ZnCl_2$ formed as a result of the in situ preparation of vinyl ketone affected the second catalytic reaction, the 1,4-conjugate addition, because in additional experiments an addition of $ZnCl_2$ (1.6 equiv.) into the reaction carried out in Entry 4 decreased the yield of **6b** to 29–37% and some of the enone **2** and organozinc **3** remained unchanged similarly to the reaction carried out in Entry 3. However, this was overcome simply by changing the addition order of the two organozincs to **4** and **1** as shown in Entry 5 to afford **6b** in 66% yield.

Diketone **6a** has been converted to one (**7**) of the 2,5-disubstituted pyrrolidine alkaloids,[13] a poison gland product of the South African ant *Solenopsis punctaticeps*.[14] Diketone **6b** has easily been transformed by a Paal–Knorr reaction[15] followed

Table 1. Preparation of unsymmetrical 1,4-diketones via a five-component connecting reaction



Entry	Reagent or substrate 1	3	4	Product 6	Yield / GC yield
1	*n*-BuZnI		*n*-heptylZnI	 **6a**	69% (89%)
2[a]			*n*-heptylZnI		70%
3	*n*-BuZnI		EtOOC–$(CH_2)_3$–ZnI	 **6b**	37%
4[a]			EtOOC–$(CH_2)_3$–ZnI		79%
5	EtOOC–$(CH_2)_3$–ZnI		*n*-BuZnI		66%

[a]Compound **3** was used in place of reagents **1** and **2**.

by an intramolecular amidation into a fused bicyclic lactam **8**, which is a common key intermediate for the synthesis of *syn*- and *anti*-substituted indolizidine alkaloids,[16] monomorine I (**9**), the trail-laying pheromone of the pharaoh ant *M. pharaonis* L., and (3*S*,5*S*,8a*R*)-3-butyl-5-(4-pentenyl)indolizine (**10**), isolated from alkaloidal venom of the New Zealand ant *M. smithii* Forel (Figure 3).[17,18]

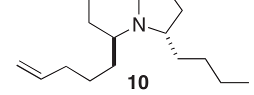


Figure 3. Reported syntheses of pyrrolidine and indolizidine alkaloids from 1,4-diketones **6a** and **6b**.

We have presented a preliminary report on preparation of 1,4-diketones via a one-pot five-component connecting reaction based on a palladium-catalyzed 1,4-acylation of organozinc halides to vinylic ketones, generated in situ from acryloyl chloride using the same palladium catalyst.

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