Preparation of 1,3-Diketones by the Reaction of Bis(iodozincio)methene with Acyl Cyanides or Palladium-Catalyzed Reaction with Acyl Chlorides

Seijiro Matsubara, Kazunari Kawamoto, and Kiitiro Utimoto*

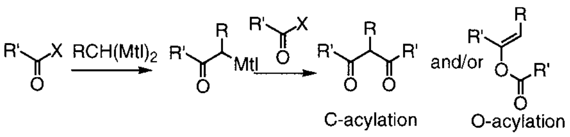
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606-8501, Japan

FAX +81 (0)75 7534863; e-mail utimoto@orgrx2.kuic.kyoto-u.ac.jp

Received 18 December 1997

Abstract: Bis(iodozincio)methane, prepared from lead-catalyzed reaction of zinc with diiodomethane, afforded 1,3-diketones either by the reaction with acyl cyanides or by palladium catalyzed reaction with acyl chlorides. Reaction with adipoyl dichloride gave cyclic enol ester by intramolecular reaction.

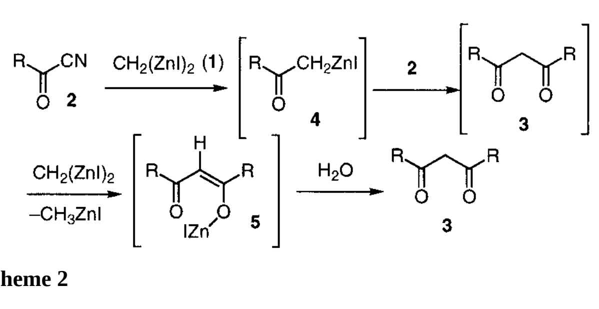
gem-Dimetallic reagents have been used as versatile reagents in organic synthesis.[1] Recent preparation of bis(iodozincio)methane (**1**) in high purity has opened novel strategies of C-C bond formation including carbonyl-olefination and three component coupling by stepwise reaction of two different electrophiles.[2–4] It is conceivable that double acylation of **1** provides a new entry to 1,3-diketones, but double acylation of dimetallic reagents containing Cu and Zn gave enol ester by O-acylation at the second step.[5]



Scheme 1

As we have found that **1** reacted with various electrophiles under Pd catalysis,[2] reaction of **1** with two acyl groups was examined. This paper describes two procedures of double acylation on **1** affording 1,3-diketones **3**; reaction with acyl cyanides **2** in THF and reaction with acyl chlorides **6** in THF-DMI under Pd catalysis.

Reaction of benzoyl cyanide (**2**, R = Ph; 2 mmol) with **1** (1 mmol) afforded 1,3-diphenyl-1,3-propanedione (**3**, R = Ph) in 44% yield. Yield of the diketone **3** was improved to 90% by the reaction of **1** with **2** in a molar ratio of 1 : 1, but reaction of **1** with **2** in a molar ratio of 1.5 : 2 gave **3** in 59% yield.[6,7] Combination of reagents ratio and the yield of **3** can be explained by equation 2; reaction of **1** with **2** gave zinciomethylated product **4**, which reacted with **2** affording 1,3-diketone **3.** Intermediary produced **3** reacted with dimetallic reagent **1** to produce stable zinc enolate **5** and methylzinc iodide. As any considerable formation of acetophenone could not be detected from the reaction mixture, reactivity of acyl cyanides **2** towards intermediary **4** is much higher than that towards any other nucleophiles in the reaction mixture; relative order of reactivity towards **2** is **4** >> **1** > methylzinc iodide. Other acyl cyanides **2** afforded the corresponding 1,3-diketones **3**. Results are summarized in Table 1.[8]



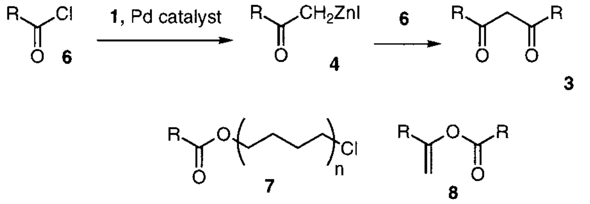
Scheme 2

Table 1. Reactions of Bis(iodozincio)methane (**1**) with Acyl Cyanides **2**

Entry	**1**	Acyl Cyanide **2**		Reaction		1,3-Diketone **3**
	mmol	R	mmol	Temp (°C)	Time (h)	Yield (%)
1	2.0	Ph	2.0	20	2	90
2	1.0	Ph	2.0	20	2	44
3	1.5	Ph	2.0	20	2	59
4	2.0	n-C_8H_{17}	2.0	20	2	85
5	1.0	n-C_8H_{17}	2.0	20	2	33
6	2.0	n-C_8H_{17}	2.0	0	6	39
7	2.0	$(CH_2)_2CO_2Et$	2.0	20	3	58
8	1.0	PhCH=CH	1.0	20	5	20[a]

[a] Besides expected diketone **3** formation, Michael addition proceeded affording a mixture of 3-phenylbutyric acid, 4-phenyl-3-oxopropanenitrile and 4-phenyl-2-oxopentanamide after hydrolytic workup

Reaction of **1** with benzoyl chloride (**6**; R = Ph) gave 4-chlorobutyl benzoate (**7**; n = 1) as a major product; zinc salt-catalyzed reaction of acyl chlorides **6** with THF proceeded mainly. Coupling reaction under Pd catalysis proceeded smoothly yielding 1,3-diketone. Ligand tuning was necessary to obtain satisfactory results, although PPh_3 gave the expected 1,3-diketone **3** in good yield. As can be seen from the results shown in Table 2, $P(C_6H_4\text{-OMe-}p)_3$ gave better results. Use of 1:1 mixture of THF-DMI depressed the formation of by-product **7** and afforded **3** exclusively in 89% yield.[9] Reaction using a bulky phosphine as a ligand proceeded sluggishly affording **7** mainly. Bidentate ligand also afforded an unsatisfactory result.



Scheme 3

In contrast to the reaction with benzoyl chloride (**6**; R = Ph), nonanoyl chloride (**6**; R = C_8H_{17}) gave a mixture of 1,3-diketone (**3**; R = n-C_8H_{17}), 4-chlorobutyl ester **7**, and O-acylated product **8**. The best yield of 1,3-diketone **3** was recorded using $P(C_6H_4\text{-OMe-}p)_3$ as a ligand and a mixture of THF-DMI (1:1) as solvent at –15 °C.

Contrary to the above intermolecular reaction, reaction of **1** with adipoyl dichloride (**9**) under Pd catalysis in THF-DMI gave cyclic enol ester **10** in 75% yield by intramolecular O-acylation of intermediary **11**.[3,10] Mechanistic studies on selective O-acylation in intramolecular reaction are underway.

Thus symmetrical 1,3-diketones can be produced from dimetallic reagent **1** and acylating agents, acyl cyanides **2** or acyl chlorides **6**, by single operation.

Table 2. Pd-Catalyzed Reaction of **1** with Benzoyl Chloride[a]

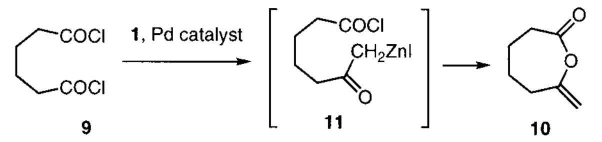
Entry	Phosphine	Time (h)	**3** (%)	**7**(%)
1	PPh_3	2	13	nd[b]
2	PPh_3	4	58	22
3	$P(2\text{-fur})_3$	2	50	1
4	$P(p\text{-tol})_3$	2	77	4
5	$P(C_6H_4\text{-OMe-}p)_3$	2	79	5
6	$P(C_6H_4\text{-OMe-}p)_3$	2	89	nd[c]
7	$P[C_6H_2\text{-}2,4,6(OMe)_3]_3$	2	5	49
8	$Ph_2P(CH_2)_4PPh_2$	4	21	64

[a]Reaction was carried out at –15 °C using **1** (2.0 mmol) and **6** (R = Ph, 2.0 mmol) in THF (15 ml) with Pd catalyst that was prepared in situ by mixing of $Pd_2(dba)_3{\bullet}CHCl_3$ (0.05 mmol) and phosphine (0.4 mmol). [b]Reaction at 20 °C. [c] A mixture of THF/DMI (1/1) was used as solvent

Table 3. Pd-Catalyzed Reaction of **1** with Nonanoyl Chloride[a]

Entry	Lignd	Solvent	Time (h)	**3** (%)	**8** (%)	**7** (%)
1	PPh_3	THF	2	10	8	12
2	$P(p\text{-tol})_3$	THF	2	20	15	20
3	$P(p\text{-tol})_3$	THF/DMI	2	62	8	nd[b]
4	$P(p\text{-tol})_3$	DMI	2	34	19	nd[b]
4	$P(C_6H_4\text{-OMe-}p)_3$	THF	2	23	25	40
5	$P(C_6H_4\text{-OMe-}p)_3$	THF/DMI	2	81	14	nd

[a]Reaction was carried out at –15 °C using **1** (2.0 mmol) and **6** (R = $n\text{-}C_8H_{17}$, 2.0 mmol) in THF (15 ml) with Pd catalyst that was prepared in situ by mixing of $Pd_2(dba)_3{\bullet}CHCl_3$ (0.05 mmol) and phosphine (0.4 mmol). [b]Reaction was carried out at room temperature



Scheme 4

Table 4. Pd-Catalyzed Reaction of **1** with Adipoyl Dichloride (**9**)[a]

Entry	Concentration of **1** (M)	Temp (°C)	Time (h)	**10** (%)
1	0.05	-15	1	38
2	0.05	0	0.5	45
3	0.05	20	0.5	75
4	0.25	-15	0.5	4

[a]Reaction was carried out with 2 mmol of **1**, 1 mmol of **9**, 0.05 mmol of $Pd_2(dba)_3$, 0.4 mmol of tris(4-methoxyphenyl)phosphine in THF-DMI

Acknowledgement: This work is supported by the Ministry of Education, Science, Sports, and Culture (Grant in Aid #09231223, #09238221).

References and Notes

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(6) Typical procedure for the production of bis(iodozincio)methane (**1**): A THF solution of bis(iodozincio)methane (**1**) was prepared according to the reported procedure with slight modification. A mixture of acid-washed and dried zinc powder (Wako Pure Chemical Industries Ltd. Japan, containing 0.04–0.07 mol % of lead; 12.3 g, 188 mmol) and THF (7.5 mL) was added with CH_2I_2 (2.0 g, 7.5 mmol) and sonicated for 15 min. THF (50 mL) was added to the mixture, and then the mixture was cooled in a ice-water bath. To the mixture, a THF (15 mL) solution of CH_2I_2 (20.1 g, 75 mmol) was added over 1 h. The reaction mixture was stirred for 1 h at 0 °C, then 1 h at room temperature. Yield of bis(iodozincio)methane (**1**) was determined by ^1H NMR using 2,2,3,3-tetramethylbutane as internal standard. Average yield of bis(iodozincio)methane (**1**) was 60%. Bis(iodozincio)methane (**1**) was also obtained in 50–60% yield by using a mixture of zinc powder (Merck Co. or Aldrich Chemical Co.) and 0.5–1 mol % of $PbCl_2$, in place of Wako zinc.

(7) Reaction of bis(iodozincio)methane (**1**) with acyl cyanide **2**: To a THF solution of **1** (3.6 mL of 0.55 M solution containing 2.0 mmol of **1**), a THF (7.0 mL) solution of benzoyl cyanide (**2**, R = Ph; 262 mg, 2.0 mmol) was added at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was added with 20 mL of 1 M aq. HCl. The mixture was extracted twice with ethyl acetate, then combined organic layer was washed, dried, concentrated, and purified by column chromatography. Dibenzoylmethane (**3**, R = Ph) was obtained in 90% yield.

(8) Reaction of **1** with α,β-unsaturated acyl cyanide (**2**; R = PhCH=CH) proceeded both acylation and Michael addition (entry 8 in Table 1). Michael addition (or conjugated addition) of **1** to α,β-unsaturated carbonyl compounds will be published in a separate paper.

(9) To a DMI (10 mL) solution of $Pd_2(dba)_3{\bullet}CHCl_3$ (0.05 mmol) and $P(C_6H_4\text{-OMe-}p)_3$ (0.4 mmol), a THF solution of **1** (3.6 mL of 0.55 M solution containing 2.0 mmol of **1**) was added. A THF solution (6 mL) of **6** (R = Ph, 263 mg, 2.0 mmol) was added dropwise to the reaction mixture maintained at –15 °C. After being stirred for 2 h, the reaction mixture was worked up as described above.

(10) A DMI-THF solution containing catalyst and **1** was prepared as described above. To the solution, a THF solution of adipoyl dichloride (**9**, 183 mg, 2.0 mmol in 10 mL THF) was added dropwise at –10 °C. The reaction mixture was stirred for 1 h, then quenched by adding 20 mL of ethyl acetate and 1.0 g of NH_4Cl powder. Product **10** was purified by distillation and chromatography.