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Conjugate addition of zincates derived from ketone α,β -dianions to enones. An access to unsymmetrical 1,6-diketones

Ilhyong Ryu,^{*,†} Masanobu Ikebe, Noboru Sonoda,[‡] Shin-ya Yamato,
Go-hei Yamamura and Mitsuo Komatsu

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

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Abstract

The conjugate addition of organozincates derived from ketone α,β -dianions to enones was examined. Good yields of unsymmetrical 1,6-diketones were obtained by this reaction. A mixed zincate consisting of the dianion and methyllithium in a 2:1 ratio gave results which were comparable to those of an unmixed dianion zincate. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: ketone α,β -dianion; dianion zincate; conjugate addition; unsymmetrical 1,6-diketone.

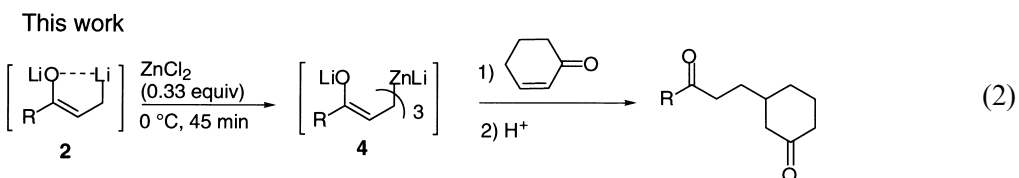
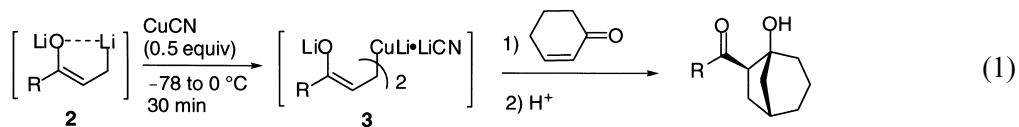
Ketone α,β -dianions **2** (the lithium enolate derivative of β -lithio ketones) can be easily prepared by methods involving the tin–lithium exchange of a β -stannyl ketone **1**.^{1,2} This provides an ideal opportunity for the investigation of the reaction behaviors of hitherto unknown types of dianionic organometallic reagents. As a result, we recently reported on the generation and reaction of dianionic cuprates **3** with enones,² which gave keto alcohols having a bicyclic structure via C–C bond formation at both the α and β positions of the dianion structure (Eq. (1)). The fact that an intramolecular lithium enolate moiety participates in the formation of the C–C bond is mechanistically intriguing, but unfortunately this hampers the use of the addition reaction as a route to the synthesis of unsymmetrical 1,6-diketones. Triorganozincates, developed by Isobe and Goto,³ are frequently used as a carbanion source in the conjugate addition to enones.⁴ In this regard, the issue of whether the related reaction behavior of dianion zincates toward enones is identical to that of the corresponding cuprates or not became of interest. In this paper we report that, unlike the corresponding cuprates **3**, the zincates **4** derived from ketone α,β -dianions

* Corresponding author. Fax: +81 722 54 9695; e-mail: ryu@ms.cias.osakafu-u.ac.jp

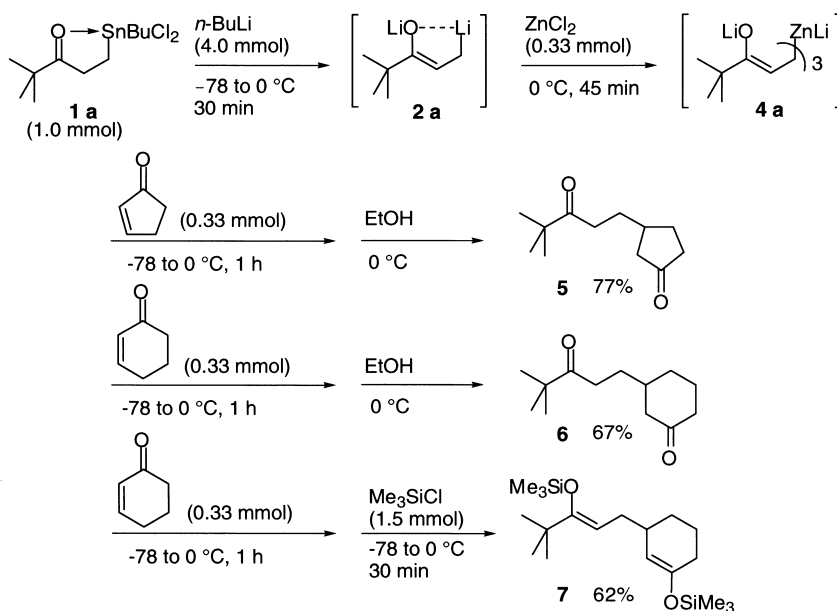
† Present address: Department of Chemistry, Faculty of Arts and Sciences, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan.

‡ Present address: Department of Applied Chemistry, Faculty of Engineering, Kansai University, Sakai, Osaka 564-0073, Japan.

undergo the normal mode of conjugate addition reaction with enones to form bis-enolate anions, thus providing a new entry to unsymmetrical 1,6-diketones (Eq. (2)).



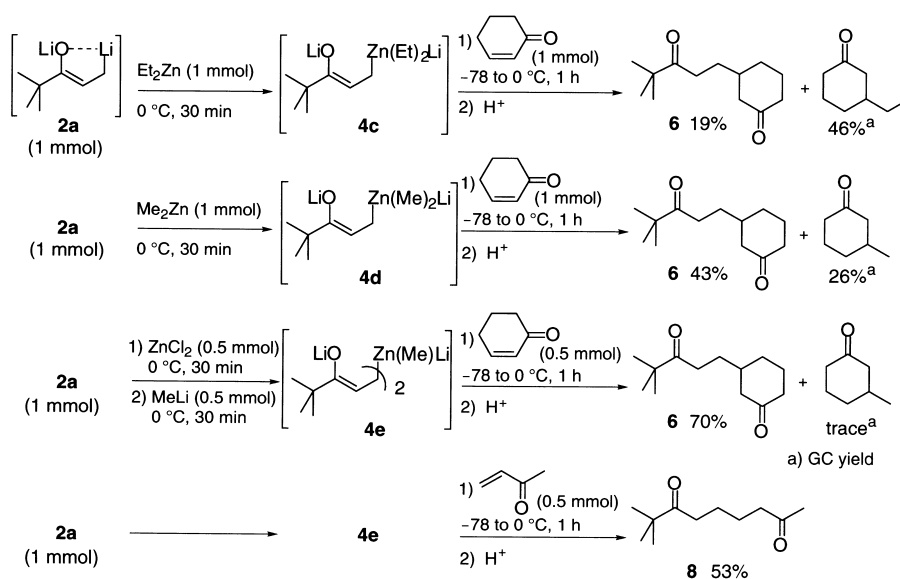
The ketone α,β -dianion **2a** was prepared by the straightforward addition of 4 equiv. of *n*-BuLi to a THF solution of 4,4-dimethyl-1-[(dichlorobutyl)stannyl]-3-pentanone (**1a**), via the procedure previously reported by us.² Thus, to a cooled solution (-78°C) of **1a** (1 mmol) was added *n*-BuLi (4 mmol). After warming to 0°C , followed by stirring for 30 min, a clear solution of **2a** was obtained. Subsequent treatment of the thus formed dianion **2a** with zinc chloride (0.33 mmol) at 0°C , followed by stirring for 45 min, led to the formation of a dianion zincate **4a**. The yellow solution containing **4a** was added to 2-cyclopenten-1-one at -78°C and warmed to 0°C . After stirring for 1 h, the reaction mixture was quenched by the addition of ethanol. Chromatographic purification of the crude product on silica gel afforded the unsymmetrical 1,6-diketone **5** in 77% yield (Scheme 1).⁵ The conjugate addition of **4a** to 2-cyclohexen-1-one also afforded the



Scheme 1.

1,6-diketone **6** in 67% yield.⁶ In both cases, bicyclic products were not found in the product mixture, suggesting that the production of bicyclic alcohols is characteristic in the case of dianion cuprates. Quenching by trimethylchlorosilane gave a bis-enol silyl ether **7** in 62% yield,⁶ which is consistent with the formation of a bis-enolate anion in this system.

In the conjugate addition chemistry of organozincate species, such as R_3ZnLi , only 1 equiv. of R is consumed in the transfer to enones, thereby leaving 2 equiv. unused. This led us to investigate the reaction of mixed zincates.⁷ The reaction of the mixed zincate **4c**, derived from a 1:1 mixture of **2a** and Et_2Zn , with cyclohexenone, resulted in a 29:71 ratio of dianion to Et transfer (Scheme 2). The use of a mixed zincate **4d**, derived from a 1:1 mixture of **2a** and Me_2Zn , led to a 62:38 ratio of dianion to Me transfer. Thus, the order of approximate reactivity based on the results herein is $Et \geq \text{dianion} > Me$. A higher yield of 1,6-diketone **6** (70%) was obtained using the mixed zincate **4e** prepared from 2 equiv. of α,β -dianion **2a** and 1 equiv. of MeLi. The reaction of **4e** with methyl vinyl ketone gave **8** in 53% yield.



Scheme 2.

In summary, the reaction of dianion zincates with enones leads to the formation of bis-enolate anions, which serve as precursors to unsymmetrical 1,6-diketones. This is in sharp contrast to that of the corresponding dianion cuprates, which gave bicyclic alcohols as major products. It was also found that a mixed zincate derived from 2 equiv. of ketone α,β -dianion and 1 equiv. of methyl lithium is a useful reagent for the selective transfer of the ketone α,β -dianion.

Acknowledgements

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5. A typical procedure for the reaction of zincates with cyclic enones: To a cooled solution (-78°C) of 4,4-dimethyl-1-[(dichlorobutyl)stannyl]-3-pentanone **1a** (358 mg, 1.0 mmol) in THF (10 ml) was added *n*-BuLi (2.59 ml, 1.54 M solution in hexane, 4.0 mmol) dropwise over a period of 5 min. This solution was allowed to warm to 0°C and stirred for 30 min. A resulting solution of the α,β -dianion **2a** was added to a solution of zinc chloride (0.33 ml, 1.0 M solution in Et_2O , 0.33 mmol) at 0°C , followed by stirring for 45 min at the same temperature. After cooling to -78°C , 2-cyclopenten-1-one (28 μl , 0.33 mmol) was added to a solution containing zincate **4a** and the resulting solution was allowed to warm to 0°C . Stirring was continued for 1 h at the same temperature and the reaction mixture was then treated with absolute ethanol and allowed to stand for 3 h. The reaction mixture was then poured into saturated aqueous NH_4Cl (40 ml). The aqueous layer was extracted with Et_2O (40 mL \times 3), and the organic extracts were combined, dried, and concentrated in vacuo. Purification by flash chromatography (elution with hexane/ Et_2O , 2:1) provided the desired 1,6-diketone **5** (50 mg, 77%) as a clear oil. $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 1.11 (s, 9H, *t*-Bu), 1.20–1.43 (m, 1H), 1.5–1.8 (m, 3H), 1.83–2.10 (m, 3H), 2.15–2.37 (m, 2H), 2.49 (t, 2H, $J=7.0$ Hz); $^{13}\text{C-NMR}$ (68 MHz, CDCl_3) δ 26.31, 29.29, 29.40, 34.34, 36.52, 38.31, 44.03, 44.89, 215.13, 218.96; EIMS m/z (relative intensity, %) 139 ($\text{M}^+-\text{C}_4\text{H}_9$, 18), 96 ($\text{M}^+-\text{C}_6\text{H}_{12}\text{O}$, 100), 57 (C_4H_9 , 97); IR (neat, cm^{-1}) 1741, 1704 ($\nu_{\text{C}=\text{O}}$); HRMS. calcd for $\text{C}_8\text{H}_{11}\text{O}_2$ ($\text{M}^+-\text{C}_4\text{H}_9$): 139.0759. Found: 139.0778.
6. Spectral data, **6**: $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 1.09 (s, 9H, *t*-Bu), 1.2–1.4 (m, 1H), 1.5–1.8 (m, 5H), 1.9–2.1 (m, 3H), 2.2–2.5 (m, 2H), 2.51 (t, 2H, $J=8.0$ Hz); $^{13}\text{C-NMR}$ (68 MHz, CDCl_3) δ 25.16, 26.44, 30.46, 31.36, 33.53, 38.67, 41.35, 44.17, 47.89, 211.43, 215.43; EIMS m/z (relative intensity, %) 153 ($\text{M}^+-\text{C}_4\text{H}_9$, 8), 110 ($\text{M}^+-\text{C}_6\text{H}_{12}\text{O}$, 90), 57 (C_4H_9 , 100); IR (neat, cm^{-1}) 1707 ($\nu_{\text{C}=\text{O}}$); Anal. calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.24; H, 10.55. Found: C, 74.11; H, 10.71. **7**: $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 0.16, 0.18 (s, 9H, Me_3Si), 1.06 (s, 9H, *t*-Bu), 1.1–1.2 (m, 1H), 1.5–1.8 (m, 3H), 1.8–1.9 (m, 4H), 1.9–2.0 (m, 1H), 4.54 (t, 1H, $J=6.9$ Hz), 4.80 (s, 1H); $^{13}\text{C-NMR}$ (68 MHz, CDCl_3) δ 0.31, 1.10, 21.85, 28.65, 28.77, 29.99, 33.37, 35.29, 36.30, 101.98, 109.36, 150.48, 158.99; EIMS m/z (relative intensity, %) 354 (M^+ , 8), 339 (M^+-15 , 58), 169 (100); IR (neat, cm^{-1}) 1661 ($\nu_{\text{C}=\text{C}}$), 1251, 843 ($\nu_{\text{Si}-\text{C}}$); HRMS. calcd for $\text{C}_{19}\text{H}_{38}\text{O}_2\text{Si}_2$: 354.2410. Found: 354.2427. Spectral data of **8** were consistent with those previously reported (Ref. 2).
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