Reductive Generation of Enolates Using a Chromium(III) Ate-Type Reagent as a Reductant and Reactions of the Enolates with Electrophiles[1]

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Summary: The chromium ate-type reagent "Bu_6CrLi_3" reacted cleanly with ketones and esters bearing a leaving group at the α-position to produce enolates under mild conditions, where the chromium ate reagent acts as a formal two-electron reductant. In a stepwise manner, the generated enolates reacted with a variety of electrophiles with high selectivity.

Chromium(II) reagents are well-recognized to be one-electron reductants and have been used for selective organic synthesis.[2] We recently found that an equimolar amount of an alkylchromium ate-type reagent, prepared from chromium(III) chloride and alkyllithium reagent, reacted as a reductant with allyl and propargyl phosphates to produce the corresponding allyl- and propargylchromium reagents, respectively, and the generated allylic and propargylic reagents reacted as nucleophiles with a variety of electrophiles.[3] In the course of our investigation on other uses of the chromium ate-type reagent in organic synthesis, we found that enolates were reductively generated by the reaction of carbonyl compounds bearing a leaving group at the α-position with an equimolar amount of a chromium ate-type reagent, where the chromium reagent serves as a formal two-electron reductant (eq 1). Previously, it was reported that α-bromo ketones, esters, and amides reacted with aldehydes and ketones in the presence of a chromium(II) reagent as a reductant to produce cross-aldol products under the Barbier-type conditions,[4] while a stepwise reaction by the so-called Grignard-type procedure was not successful; namely, after the generation of enolates from bromo ketone with chromium(II) in the absence of an electrophile, the enolate was not trapped with the electrophile.[5] We describe here the reductive generation of enolates by a chromium ate reagent and characteristic features in the Grignard-type reactions of the generated enolates with a variety of electrophiles.

(1)

1a: R^1 = Et, R^2 = Me, R^3 = H, X = Br
1b: R^1 = Ph, R^2 = Me, R^3 = H, X = OAc
1c: R^1 = Ph, R^2 = Me, R^3 = Me, X = OAc
1d: R^1 = OEt, R^2 = Me, R^3 = H, X = Br
1e: R^1 = OEt, R^2 = Me, R^3 = Me, X = Br

2

2-Bromo-3-pentanone (**1a**; 0.50 mmol) was added to a solution of "Bu_6CrLi_3"[6,7] (0.52 mmol) in THF (4 mL) at −78 °C, and the reaction mixture was stirred at the same temperature. After 1 h, benzaldehyde (3.6 mmol) was added to the mixture at −78 °C, and the resulting mixture was stirred for 10 min. After conventional workup, the cross-aldol adduct **2a** was obtained in 88% yield.[8] Other results of this type of reaction are compiled in Table 1. Interestingly, with regard to aromatic ketones, an acetoxy group also serves as a leaving group, similarly to a bromo group of **1a**. When α-acetoxypropiophenone (**1b**) was treated with the chromium ate reagent at −20 °C for 1 h, and the reaction was quenched with propionaldehyde at −78 °C for 10 min, the corresponding aldol adduct **2b** was obtained in 82% yield (syn/anti = 75/25) (entry 2).[9] The "enolate" of the α-disubstituted ketone was generated in a similar manner (entry 4). From α-bromo esters **1d** and **1e**, ester enolates were also generated (entries 5−10). The enolates thus generated reacted with a variety of aldehydes and even ketones. The results shown in Table 1 deserve some comment. "Bu_6CrLi_3" selectively reacts toward the halo part of halo carbonyl compounds as a reductant,

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[5] (a) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829−3830. (b) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561−568.

[6] The tentatively used formula "Bu_6CrLi_3" expresses only the molar ratio of butyllithium employed to chromium(III) salt, since the structures of the species are not clear at present. The reagent "Bu_6CrLi_3" was prepared as follows: to a suspension of ground chromium(III) chloride (0.52 mmol) in THF (4.0 mL) was slowly added a solution of butyllithium in hexane (3.12 mmol/1.99 mL; 1.57 M) at −78 °C under argon with stirring. The resultant mixture was further stirred for 30 min at the same temperature.

[7] "Bu_6CrLi_3" is possibly in equilibrium between "Bu_5CrLi_2" and BuLi. When **1a** was treated with "Bu_5CrLi_2" at −78 °C, the reduction took longer time (∼3 h) for consumption of **1a**, while after quenching with benzaldehyde, almost the same yield of **2a** (87%, syn/anti = 63/37) was obtained. "Bu_5CrLi_2" may be in other equilibria for disproportionation between "Bu_6CrLi_3" and "Bu_4CrLi". A reaction of **1a** with "Bu_4CrLi" at −78 °C for 1 h, after quenching with benzaldehyde, gave 34% of **2a** (syn/anti = 56/44).

[8] The reaction conditions were not fully optimized, and the amount of electrophiles may be reduced.

[9] For aliphatic ketones, an acetoxy group did not work for the generation of enolates.

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Table 1. Generation of Enolates from 1 and Reaction of the Enolates with Carbonyl Compounds[a]

entry	substrate **1**	redn conditions	carbonyl compd	product **2**	
					% yield[b] (*syn*/*anti*)[c]
1	**1a**	−78 °C, 1 h	PhCHO	**2a**	88 (68/32)
2	**1b**	−20 °C, 1h	EtCHO	**2b**	82 (75/25)
3			*i*-PrCHO	**2c**	77 (71/29)
4	**1c**	−20 °C, 1 h	PhCHO	**2d**	85
5	**1d**	−40 °C, 1 h	HexCHO	**2e**	88 (80/20)
6			$\mathrm{Bu_2CO}$	**2f**	80
7	**1e**	−20 °C, 1 h	HexCHO	**2g**	95
8			*c*-HexCHO	**2h**	79
9			2-furylCHO	**2i**	96
10			$\mathrm{Bu_2CO}$	**2j**	97

[a] All reactions were carried out under conditions shown in the table, using 0.5 mmol of the substrate. Aldol reactions were carried out at −78 °C for 10 min using 7 equiv of the electrophile. Reactions were quenched with saturated $\mathrm{NH_4Cl}$ solution. [b] Isolated yield. [c] Syn/anti ratio was determined by ^{1}H NMR.

not as an alkylation agent. For all reactions, only an equimolar amount of the chromium reagent was used.[10] The present reduction conditions for the generation of enolates are extremely mild, compared to those for the Barbier-type reactions using chromium(II). The mild conditions would probably be beneficial to prevent the abstraction of hydrogen in the generation of enolates. The clean generation of enolates made the stepwise procedure possible, and the following reactions of enolates with electrophiles could also be conducted under mild conditions. As for the stereochemistry, both enolates, irrespective of ketone enolates or ester enolates, uniformly provided *syn*-aldol adducts, selectively in all cases, and these results are in marked contrast to the selectivity in the reported Barbier-type reactions.[11] Butylation of the produced aldolates by a butylchromium reagent was not observed in these reactions.

Although it is not clear at the moment whether the enolates generated here are chromium enolates or not, the following interesting feature in the reactivity of the enolates has emerged. When a reaction of the enolate derived from bromo ester **1e** with 2-cyclohexen-1-one was examined, the 1,4-adduct **2k** was obtained in 60% yield as a major isomer, along with the corresponding 1,2-adduct (eq 2). Such a preferential conjugate addition suggests that the present enolates are not simple lithium enolates.[12]

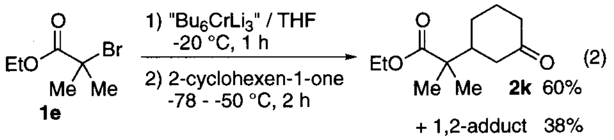
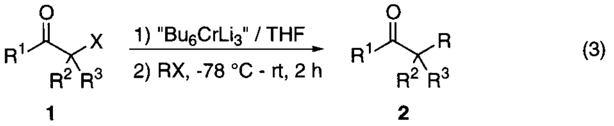


Table 2. Generation of Enolates from 1 and Reaction of the Enolates with Alkyl Halides[a]

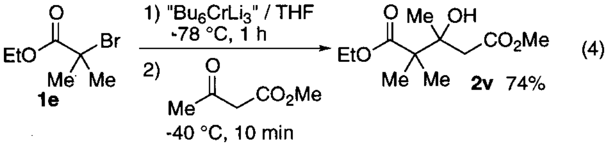
entry	substrate **1**	alkylation conditions	alkylation agent	product **2**	
					% yield[b]
1	**1b**	−20 °C, 1 h	BnBr[c]	**2l**	68
2			$\mathrm{MeO_2CCH_2Br}$	**2m**	69
3			OctI	**2n**	60
4	**1d**	−40 °C, 1 h	$\mathrm{HC{\equiv}CCH_2Br}$	**2o**	62
5			OctI[c]	**2p**	77
6	**1e**	−78 °C, 1 h	$\mathrm{HC{\equiv}CCH_2Br}$	**2q**	87
7			$\mathrm{H_2C{=}CHCH_2Br}$	**2r**	86
8			$\mathrm{NCCH_2Br}$	**2s**	82
9			OctI[d]	**2t**	96
10			HexOTf[d]	**2u**	80

[a] *N*-methyl-2-pyrrolidinone (NMP; 2 mL) was added as an additive to the generated enolate, and the mixture was stirred for 5 min at the same temperature. An alkylating agent (7 equiv) was added at −78 °C, and the temperature of the mixure was raised to room temperature for 2 h. Reactions were quenched with saturated $\mathrm{NH_4Cl}$ solution. [b] Isolated yield. [c] HMPA was used instead of NMP. [d] No additive was used.

Chromium-mediated reactions between halo carbonyls and alkyl halides have not been reported. Reactions with several alkylating agents were also examined (eq 3, Table 2). Enolates reacted with bromides, such as benzyl bromide, bromoacetate, allyl bromide, propargyl bromide, and bromoacetonitrile, in the presence of an additive, HMPA or *N*-methyl-2-pyrrolidinone (NMP), while with iodide or triflates, simple and even less reactive alkylating agents could be used without any additives. Octyl and hexyl groups were successfully introduced to the parent carbonyl compounds (entries 9 and 10). The basicity of the present enolates seems to be low, and polyalkylation products were not found in these reactions.



In the reactions with bifunctional molecules, enolates generated by the present procedure showed chemoselectivity. In the reaction with a keto ester, a keto group selectively reacted with the enolate derived from **1e** (eq 4). Some chemoselective reactions were previously reported under Barbier conditions with chromium(II) as a reductant,[4b,d] while under those conditions, aldimines were reported to be unreactive or far less reactive compared with aldehydes.[13] In marked contrast to those reports, the enolates generated here reacted toward tosylimines comparably to aldehydes under the present conditions to give the corresponding adduct **2w** in 88% yield (eq 5). In general, reactive electrophiles tend to



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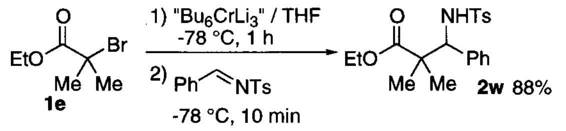
(10) In the present procedure, an excess amount of the reductant is not necessary, possibly because the reaction mixture is nearly homogeneous.

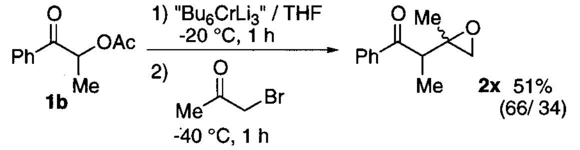
(11) Aldol-type reactions of halo ketones with aldehydes under Barbier-type conditions were reported to be *syn*-selective,[4a] while those of esters and amides were *anti*-selective.[4b,e] Although it is premature to discuss about the difference in selectivity with those of previously reported reactions, the difference may possibly come from reaction conditions and/or the different environments around the chromiums of the chromium enolates. If the chromium has many ligands and the aldol reaction proceeds through the open TS, the reaction becomes *syn*-selective.

(12) For comparison with eq 2, we examined the reaction of lithium enolate with enone. The reaction of lithium enolate generated from ethyl isobutyrate (with lithium diisopropylamide in THF at −20 °C for 1 h) and 2-cyclohexen-1-one at −78 to −50 °C for 2 h gave 82% of the 1,2-adduct and 9% of the 1,4-adduct **2k**.



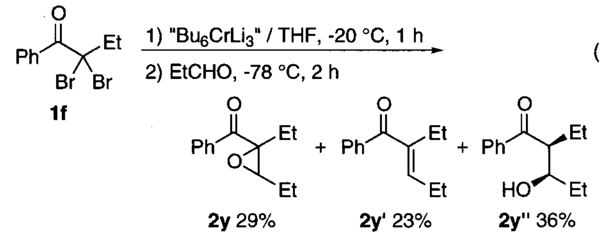
(5)

be easily reduced because of their low LUMO. Therefore, the wide reactivity of chromium enolates would possibly be hidden by the Barbier-type conditions. A salient feature of the present reaction is illustrated by the reaction of **1b** with α-bromoacetone, which may possibly be reduced to the corresponding enolate of acetone with ease (eq 6). An enolate generated from **1b** reacted with



(6)

the *halo ketone* preferentially at its carbonyl carbon. Such a "cross-type" reaction would be difficult to realize under the Barbier conditions. In the reaction of α-dibromobutyrophenone **1f** with propionaldehyde, a mixture of epoxy ketone **2y**, α,β-enone **2y′**, and β-hydroxy ketone **2y″** was obtained (eq 7).The chromium ate-type reagent reacted with ketones and esters bearing a



(7)

leaving group at the α-position to produce enolates efficiently, under mild conditions, where in contrast to the chromium(II) reagent, the chromium ate reagent acts as a formal two-electron reductant. By virtue of this reaction, the generation step and the reaction step of enolates could be separated, and both steps could be conducted under mild conditions. High reactivity of the generated enolates and their selective reactions were revealed under the mild conditions. More synthetic applications of chromium enolates will be realized by the present stepwise procedure, and further study on the enolates is now in progress.

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Supporting Information Available: Text giving experimental procedures and ^{1}H and ^{13}C NMR, IR, and mass spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In previous reports,[4b,d] chemoselectivity under the Barbier-type conditions was examined by the intermolecular competitive reactions with aldehydes. In these experiments, it was reported that only ketones competed with aldehydes (to aldehyde/to ketone = (7−30)/1), and with other electrophiles such as Michael acceptors, imines, alkyl halides, and even more reactive Eschenmoser's salt, no products derived from these electrophiles were formed under the conditions. Therefore, it is uncertain whether these less reactive electrophiles react with halo ketones and halo esters *in the absence of* competing aldehydes under Barbier conditions.