

Preparation of Enolates from α -Haloketones with *n*-BuLi, PhMgBr, or Et₂Zn via Halogen-Metal Exchange Reaction

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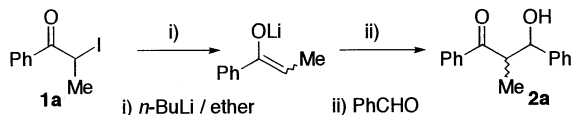
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Metal-halogen exchange of α -iodoketones was performed upon treatment with *n*-BuLi, PhMgBr, Et₂Zn or Me₃Al in ether at 0 °C to give the corresponding metal enolates which reacted with aldehydes to provide the aldol type products in good yields.

The aldol type condensation is one of the most versatile synthetic methods in organic chemistry. Many methods for the preparation of metal enolates are known.¹ Among them, an abstraction of an acidic hydrogen on a carbon adjacent to carbonyl carbon with basic metal-containing reagents such as LDA and oxidative metallation² of α -halocarbonyl derivatives with metal provide two important and general methods for preparation of metal enolates. In the latter case, zinc metal³ is a choice and other metal such as Li or Mg tends to fail because product and/or the starting material are highly reactive under the reaction conditions to give side reaction products. Here we wish to report an alternative facile and general route to various metal enolates from α -haloketones via halogen-metal exchange.⁴

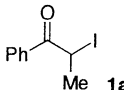
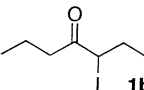
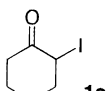
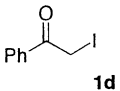
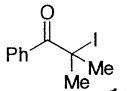
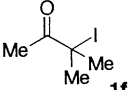
An addition of butyllithium (1.2 mmol) to an ethereal solution of α -iodopropiophenone (**1a**) at 0 °C generated a lithium enolate which gave an aldol adduct **2a** in 73% yield upon treatment with benzaldehyde (Scheme 1).

Scheme 1.



It is worth noting that nucleophilic attack on carbonyl carbon or carbon bearing iodine did not compete with metal-halogen exchange reaction. The solvent played a critical role for the successful reaction. Thus, the use of THF in place of ether resulted in a formation of a complex mixture containing the products derived from the nucleophilic attack of butyl group on carbonyl carbon or carbon having iodine. Hexane and toluene gave the satisfactory results as well as ether and gave **2a** in 71% and 56% yield, respectively. *tert*-Butyllithium was slightly less effective than *n*-BuLi for the formation of enolates. For instance, treatment of **1b** with *t*-BuLi in ether followed by an addition of benzaldehyde gave aldol adduct *n*-PrCOCH(Et)CH(OH)Ph in 50% yield along with an unidentified complex mixture. Reaction temperature did not affect the yield of the reaction so much and the reaction between **1a** and benzaldehyde provided **2a** in 70% at 25 °C or 64% at -20 °C. The reactivity of α -bromopropiophenone decreased compared to α -iodo compound **1a** and the reaction of α -bromopropiophenone with butyllithium followed by an addition of benzaldehyde gave **2a** in 56% under the same reaction conditions. In a similar fashion, magnesium, zinc, aluminum, and boron enolates could be prepared starting from α -iodoketones with the corresponding organometallic reagents. The representative results are shown in Table 1.

Table 1. Aldol reaction of enolates derived from α -iodoketones and organometallic reagents^a

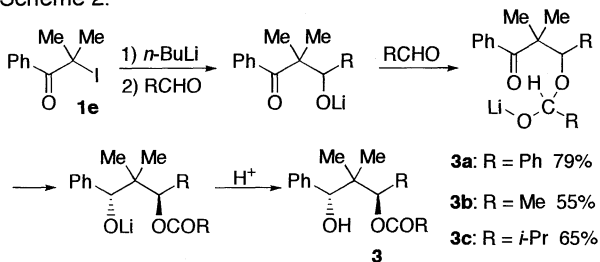
Substrate	RMtl	Aldehyde	Product Yield/%	Ratio of erythro/threo
	<i>n</i> -BuLi	PhCHO	73	39/61
	EtMgBr	PhCHO	73	43/57
	Et ₂ Zn	PhCHO	73	50/50
	Me ₃ Al	PhCHO	79	13/87
	Et ₃ B	PhCHO	97	64/34
	<i>n</i> -BuLi	<i>n</i> -C ₆ H ₁₃ CHO	51	45/55
	PhMgBr	<i>n</i> -C ₆ H ₁₃ CHO	75	64/36
	Et ₂ Zn	<i>n</i> -C ₆ H ₁₃ CHO	74	45/55
	Me ₃ Al	<i>n</i> -C ₆ H ₁₃ CHO	72	51/49
	Et ₃ B	<i>n</i> -C ₆ H ₁₃ CHO	85	27/73
	<i>n</i> -BuLi	PhCHO	73	25/75
	EtMgBr	PhCHO	81	39/61
	Et ₂ Zn	PhCHO	90	44/56
	Me ₃ Al	PhCHO	74	18/82
	Et ₃ B	PhCHO	88	61/39
	<i>n</i> -BuLi	PhCHO	40	44/56
	EtMgBr	PhCHO	67	34/66
	Et ₃ B	PhCHO	87	26/74
	Et ₂ Zn	PhCHO	79	
	Me ₃ Al	PhCHO	63	
	Et ₃ B	PhCHO	65	
	EtMgBr	PhCHO	79	
	Me ₃ Al	PhCHO	65	
	EtMgBr	CH ₃ CHO	55	
	EtMgBr	<i>i</i> -PrCHO	65	
	EtMgBr	<i>n</i> -C ₆ H ₁₃ CHO	89	

^a α -Iodoketone (1.0 mmol), RMtl (1.2 mmol), and R⁴CHO (1.0 mmol) were employed. The reaction was performed at 0 °C.

The stereochemistry (ratio of *erythro*/*threo*) of aldol adducts depends on the nature of the metal employed. The relative facility of halogen-metal exchange reaction depends on the structure of α -iodoketones. Secondary iodides **1a**, **1b**, and **1c** afforded enolates effectively upon treatment with various organometallic reagents such as *n*-BuLi, RMgBr,⁵ Et₂Zn, Me₃Al, and Et₃B.⁶

In contrast, treatment of primary iodide **1d** with *n*-BuLi followed by stirring with benzaldehyde gave an unidentified complex mixture due in part to the competitive nucleophilic attack of butyl anion on carbonyl carbon or carbon bearing iodine.⁷ The use of PhMgBr instead of *n*-BuLi provided the aldol adduct **2b** (PhCOCH₂CH(OH)Ph) in only 13% yield. However, iodine-metal exchange took place smoothly with less nucleophilic reagents such as Et₂Zn, Me₃Al, and Et₃B and aldol reaction proceeded easily with these metal enolates to give **2b** in good yields. Then, the behaviour of tertiary iodides **1e** and **1f** was examined. In the case of tertiary iodides, the nature of metal employed affected the product distribution. For instance, treatment of **1e** (1.0 mmol) with *n*-BuLi (1.2 mmol) followed by an addition of benzaldehyde (2.0 mmol)⁸ provided diol monoester **3a** as a single *anti* diastereomer (1*R**,3*R**) in good yield. The diol monoester **3a** could be produced through aldol reaction and successive Tishchenko reaction. An addition of acetaldehyde or isobutyraldehyde gave the corresponding 1,3-diol monoester **3b** (1*S**,3*R**) or **3c** (1*S**,3*R**), respectively (Scheme 2).⁹ The use of other organometallic reagents in place of *n*-BuLi prevented the Tishchenko reaction and afforded normal Reformatsky type products. Thus, EtMgBr, Me₃Al, and Et₃B afforded **2c** (PhCOC(Me)₂CH(OH)Ph) in 75%, 65%, and 59% yield, respectively. Et₂Zn gave a mixture of Tishchenko product **3a** (32%) and Reformatsky reaction product **2c** (32%).

Scheme 2.



Representative experimental procedure is as follows. Butyllithium (1.5 M hexane solution, 0.8 mL, 1.2 mmol) was added to a solution of α -iodopropiophenone¹⁰ (0.26 g, 1.0 mmol) in ether (5 mL) at 0 °C. The solution turned pale yellow after being stirred for 5 min at 0 °C. Benzaldehyde (106 mg, 1.0 mmol) was added and the whole was stirred for another 15 min at 0 °C. The resulting mixture was poured into saturated aqueous NH₄Cl and extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residual oil was submitted to silica gel column chromatography to give PhCOCHMeCH(OH)Ph (**2a**,¹¹ 0.18 g) in 73% yield as a diastereomeric mixture (*erythro*/*threo* = 39/61).

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References and Notes

- H. B. Meikelburger, C. S. Wilcox, C. H. Heathcock, B. M. Kim, S. F. Williams, S. Masamune, M. W. Rathke, P. Weipert, and I. Paterson, "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol 2, Chap. 1.4–1.9, pp. 99–320.
- E. Negishi, "Organometallics in Organic Synthesis," John Wiley & Sons, New York (1980), Vol. 1, Chap. 2, pp. 30–59.
- Reformatsky reaction: M. W. Rathke, in "Organic Reactions," John Wiley & Sons, New York (1975), Vol. 22, Chap. 4, pp. 423–460.
- Recently we have found that treatment of α -bromo- α -silyl ketones with butyllithium gave α -silyl enolates via lithium-bromine exchange. H. Shinokubo, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **35**, 3741 (1994). The reaction of α -bromoesters with Et₂Zn giving zinc enolate has been reported. M. M. Hansen, P. A. Bartlett, and C. H. Heathcock, *Organometallics*, **6**, 2069 (1987). An attempt to obtain metal enolates from ethyl α -iodopropanoate with *n*-BuLi or PhMgBr resulted in failure.
- PhMgBr and EtMgBr were equally effective for the preparation of magnesium enolates.
- In the case of Et₃B, enolates might be produced through radical mechanism instead of metal-halogen exchange. K. Nozaki, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, **64**, 403 (1991).
- The use of *t*-BuLi instead of *n*-BuLi also resulted in a formation of an unidentified complex mixture. Moreover, an inverted addition of α -iodoketone **1d** to a solution of *n*-BuLi in ether did not improve the yield of **2b**.
- The use of 1.0 mmol of benzaldehyde decreased the yield of **3a** (45%). However, aldol adduct **2c** could not be observed in the reaction mixture.
- The formation of **3** as a single diastereomer might be explained in the same fashion as described in samarium-catalyzed intramolecular Tishchenko reduction of β -hydroxy ketone. D. A. Evans and A. H. Hoveyda, *J. Am. Chem. Soc.*, **112**, 6447 (1990).
- α -Iodoketones were prepared by treatment of the corresponding α -bromoketones with NaI in acetone at 25 °C (60–80% yields). α -Bromoketones were generated according to the reported procedure (P. A. Levene, *Org. Syn.*, Coll. Vol. 2, 88 (1966)).
- C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).