The Cross-Coupling Reaction of Aldehydes with α-Diketones by the Use of Bismuth Trichloride and Metallic Zinc

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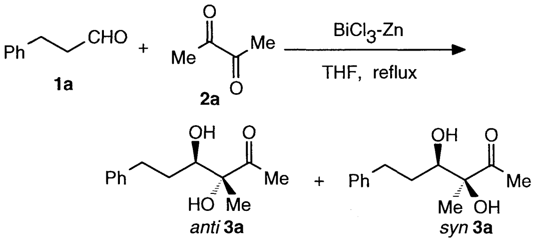
In the presence of bismuth trichloride and metallic zinc, α-diketones react with aldehydes in THF under reflux to afford the corresponding α,β-dihydroxyketones in moderate to good yields. It was also found that the present reaction proceeds smoothly by using a catalytic amount of bismuth trichloride to give the corresponding adducts. The present reaction takes place even in aqueous media.

Reductive coupling reaction between α-diketones and carbonyl compounds is a useful method to construct 1,2,3-trioxy units. To our knowledge, however, there have been a few reports on this reaction so far,[1-6] and it is still important to find a more efficient method.

In the course of our continuous investigations on the organic synthetic reaction with metallic bismuth or bismuth compounds,[7] the reductive coupling reaction of α-diketones with aldehydes by the use of bismuth compounds was tried; so far the usable starting materials have been limited to allylic halides[7] or α-halo carbonyl compounds.[8] Now it was found that the reductive cross-coupling reaction of α-diketones with aldehydes proceeded smoothly .

First, the reaction of 2,3-butanedione (**2a**) with 3-phenylpropanal (**1a**) was examined under various reaction conditions. Using bismuth trichloride ($BiCl_3$) and metallic zinc system,[7] the α-diketone was reacted with the aldehyde in THF at room temperature for 24 h to afford the corresponding α,β-dihydroxyketone **3a** in low yield (28%, *anti* **3a** : *syn* **3a** = 42 : 58). When the reaction was carried out under reflux condition for only 40 min, the yield increased in 85% with the ratio of *anti* **3a** : *syn* **3a** = 74 : 26 (Eq. 1). Metallic bismuth, $BiCl_3$-Fe(0), or $BiCl_3$-Al(0) system gave no good results and $BiCl_3$-Zn(0) was a superior system. It is noteworthy that only a catalytic amount of $BiCl_3$ was needed to effect the present reaction. The reaction of 2,3-butanedione (**2a**) with 3-phenylpropanal (**1a**) using a catalytic amount of $BiCl_3$ (0.3 equivalent to **2a**) gave the corresponding adduct **3a** in 57% yield (*anti* **3a** : *syn* **3a** = 61 : 39) after stirring for 2 h. Noteworthy is the fact that no corresponding products were obtained in the absence of $BiCl_3$.



(1)

$BiCl_3$ 2.1 equiv. Zn 5.5 equiv. ; 85 % yield (*anti***3a** : *syn***3a** = 74 : 26)
$BiCl_3$ 0.3 equiv. Zn 2.3 equiv. ; 57 % yield (*anti***3a** : *syn***3a** = 61 : 39)
Each amount was mol equivalent to 2,3-butanedione (**2a**)

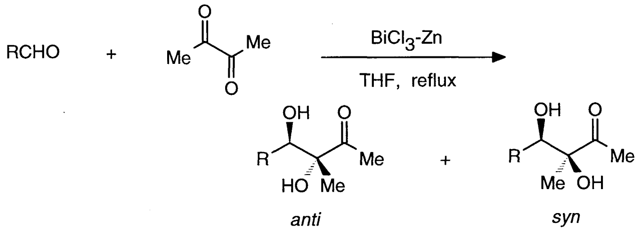


Table 1. Reaction of 2,3-butanedione with several aldehydes

Entry	Aldehyde	Yield/%	*anti* : *syn*[a]
1	$PhCH_2CH_2CHO$	85	74 : 26
2	PhCHO	63	68 : 32
3	$CH_3(CH_2)_7CHO$	61	68 : 32

[a] The ratio of *anti* : *syn* was determined by ^1H NMR.

Next, the scope and limitation of this reaction was investigated using various α-diketones and several aldehydes. As shown in Table 1, aliphatic normal-chain aldehydes reacted with 2,3-butanedione (**2a**) to afford the corresponding adducts in good yields (Entries 1 and 3), while those with alkyl branches at the α-position gave poor yields. Benzaldehyde is usable to obtain the desired product (Entry 2).[9] As shown in Table 2, not only dialkyl α-diketones but also α-ketoester such as methyl pyruvate reacted smoothly with 3-phenylpropanal (**1a**) to give the corresponding products in moderate to good yields.[9]

Further investigation revealed that the present reaction proceeded smoothly even in the presence of a proton source such as water. As shown in Eq. 2, by using commercially available phenylglyoxal monohydrate (**2b**), the reaction took place smoothly at room temperature to give the desired adduct (63% yield, *anti* **3b** : *syn* **3b** = 59 : 41). Furthermore, aqueous solution of methylglyoxal (**2c**) reacted with 3-phenylpropanal (**1a**) to afford the corresponding product in 46% yield with the ratio of *anti* **3c** : *syn* **3c** = 66 : 34 (Eq. 3).

Finally, it is noted that the present reaction takes place in aqueous media. Further application of the present reaction is now in progress.

A typical procedure is described as follows: Under an argon atmosphere, 2,3-butanedione (0.0488 g, 0.567 mmol) and 3-phenylpropanal (0.113 g, 0.843 mmol) was added to a THF (10 ml) suspension of bismuth trichloride (0.375 g, 1.19 mmol) and metallic zinc (0.203 g, 3.11 mmol) at room temperature. After stirring for 40 min under reflux, the reaction mixture was quenched by hydrochloric acid (1 M, 10 ml). Organic materials were extracted with diethyl ether three times,

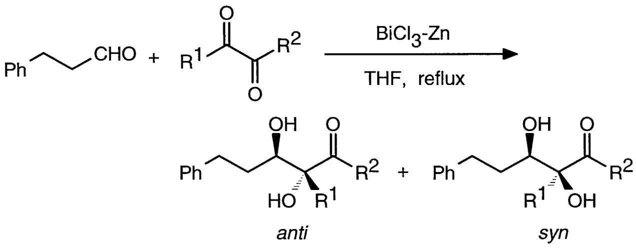
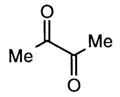
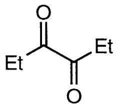
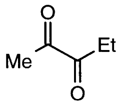
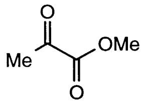
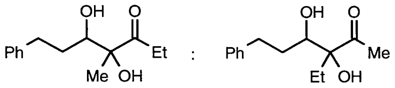


Table 2. Reaction of 3-phenylpropanal with several α-diketones

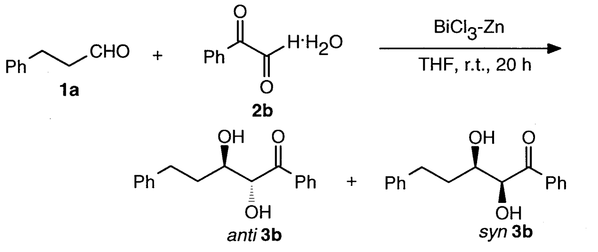
Entry	α-Diketone	Yield/%	*anti* : *syn*[a]
1		85	74 : 26
2		63	85 : 15
3		93 (71 : 29)[c]	74 : 26 [b]
4		54	67 : 33

[a] The ratio was determined by ^{1}H NMR.
[b] The ratio in the major isomer.
[c] The structure of major regioisomer : minor one was as follows:

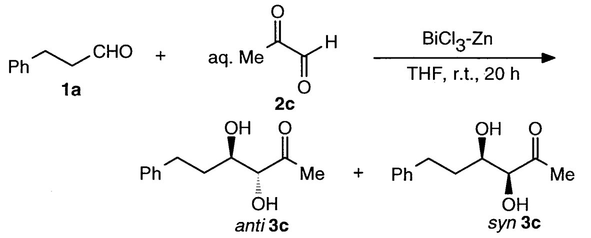


and combined organic layers were washed successively with water and brine, and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by thin layer chromatography on silica gel (hexane : AcOEt = 3 : 2) to give the diastereomeric mixture of 3,4-dihydroxy-4-methyl-1-phenyl-5-hexanone (0.107 g, 85.1% yield). The ratio of diasteromer was determined by 400 MHz ^{1}H-NMR spectra of the mixture of *anti* **3a** and *syn* **3a**. The each configuration was estimated following the method described in Refs. 5 and 6.

We thank the Center for Cooperative Reseach of The University of Tokushima for opportunities to record 400 MHz ^{1}H-NMR spectra.



63% (*anti* : *syn* = 59 : 41) (2)



46% (*anti* : *syn* = 66 : 34) (3)

References and Notes

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7 We have already discovered the first example of the Grignard-type allylation of aldehydes with allylic halides using metallic bismuth, $BiCl_3$-Zn(0), $BiCl_3$-Fe(0), or $BiCl_3$-Al(0); M. Wada and K. Akiba, *Tetrahedron Lett.*, **26**, 4211 (1985); M. Wada, H. Ohki, and K. Akiba, *Tetrahedron Lett.*, **27**, 4771 (1986); M. Wada, H. Ohki, and K. Akiba, *J. Chem. Soc., Chem. Commun.*, **1987**, 708; M. Wada, H. Ohki, and K. Akiba, *Bull. Chem. Soc. Jpn.*, **63**, 1738 (1990).
8 M. Wada, H. Ohki, and K. Akiba, unpublished results. Recently, Reformatsky-type reaction by means of $BiCl_3$-$LiAlH_4$ system was reported; Y. Aoki, K. Oshima, and K. Utimoto, 67th Annual Meeting of the Chemical Society of Japan, Tokyo, March 1994, Abstr. No. 4J207.
9 In the similar cross-coupling reaction by the use of samarium diiodide, benzaldehyde is unusable as a substrate because benzaldehyde gives the self-coupling product predominantly rather than the cross-coupling product. See Ref. 5. Methyl pyruvate also gives the similar result by the use of SmI_2.