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A Facile Synthesis of 2,3-Dihydroxyketones from 1,2-Diketones and Aldehydes Using Samarium Diiodide

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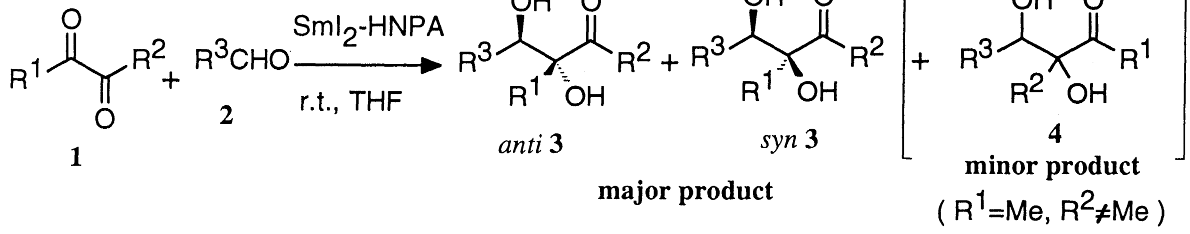
In the presence of samarium diiodide, 1,2-diketones react with aldehydes to afford the corresponding 2,3-dihydroxyketones in good yields with moderate diastereoselectivity. The reaction of unsymmetrical 1,2-diketones with aldehydes gives the products with high regioselectivities.

Aldol reaction between enediolates generated from 1,2-diketones and carbonyl compounds is a useful method to construct 1,2,3-trioxy units. However, to our knowledge, there have been few reports on this reaction so far,[1-3] and it is still important to find a more efficient method.

In the course of our investigation on the reaction with samarium diiodode (SmI_2), SmI_2 was found to mediate the enantioselective reduction of benzil.[4] The reaction is considered to proceed *via* samarium 1,2-diphenylethene-1,2-diolate. This prompted us to use such samarium enediolate for carbon-carbon bond-forming reaction with carbonyl compounds. In this communication are reported the preliminary results on the reductive aldol reaction of 1,2-diketones promoted by SmI_2.

The reaction of 2,3-butanedione (**1a**) and 3-phenylpropanal (**2a**) was examined under various reaction conditions. When a SmI_2 solution was added to a THF solution of **1a** and **2a** at room temperature under an argon atmosphere, the corresponding product was obtained in 57% yield with the ratio of *anti* **3a** : *syn* **3a** = 66 : 34 (Eq. 1). By the addition of hexamethylphosphoric triamide (HMPA, 1 mol equiv. to SmI_2),[4,6] the yield was increased to 83% with the ratio of *anti* **3a** : *syn* **3a** = 83 : 17. Though SmI_2 generally promotes the self-coupling reaction of aldehydes or ketones,[7] in this system the aldol reaction between aldehyde and 1,2-diketone proceeded almost exclusively and the self-coupling of the aldehyde **2a** hardly occurred.

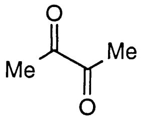
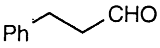
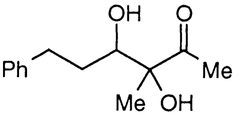
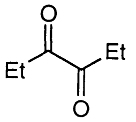
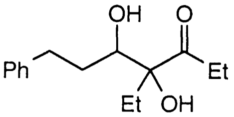
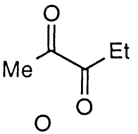
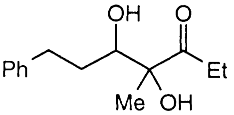
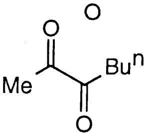
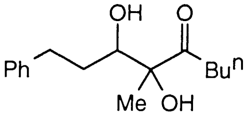
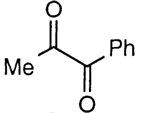
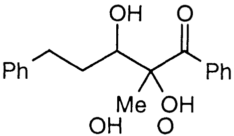
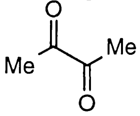
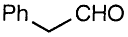
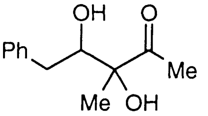
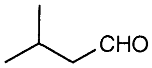
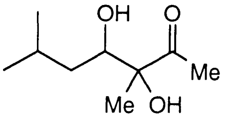
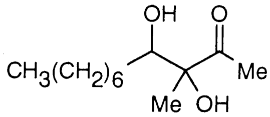
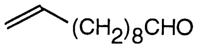
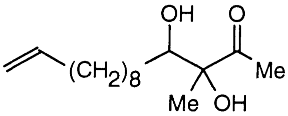
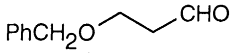
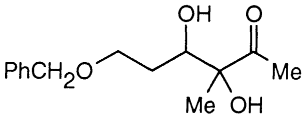
Next, the generality of this reaction system was examined using various 1,2-diketones and aldehydes and the results are shown in Table 1. Under similar conditions, not only dialkyl 1,2-diketones (Entries 1-4)



(1)

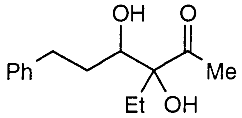
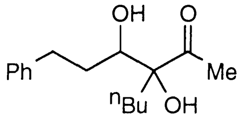
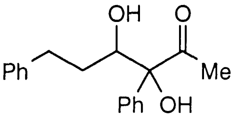
1a ; R^1, R^2 = Me, **2a** ; R^3 = $PhCH_2CH_2$ 83% (*anti* **3a** : *syn* **3a** = 83 : 17)

Table 1. Reductive coupling reactions between 1,2-diketones and aldehydes

Entry	1,2-Diketone **1**	Aldehyde **2**	Product **3**[b]	Yield / %[a]	*anti* **3** : *syn* **3**[d]
1	 **1a**	 **2a**	 **3a**	83	83 : 17
2	 **1b**		 **3b**	78	81 : 19
3	 **1c**		 **3c**	94 (85 : 15)[c]	88 : 12
4	 **1d**		 **3d**	95 (96 : 4)[c]	87 : 13
5	 **1e**		 **3e**	66 (93 : 7)[c]	>95 : 5
6	 **1a**	 **2f**	 **3f**	77	82 : 18
7		 **2g**	 **3g**	85	83 : 17
8		$CH_3(CH_2)_6CHO$ **2h**	 **3h**	82	80 : 20
9		 **2i**	 **3i**	86	78 : 22
10		 **2j**	 **3j**	76	64 : 36

a) Isolated yields. In Entries 3,4, and 5, total yield of **3** and **4**.

b) In Entries 3, 4, and 5, products **3** are major regioisomers, and minor isomers **4** are as follows:

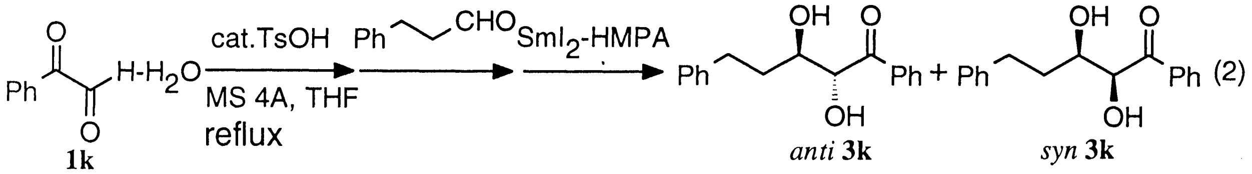
4c ;  4d ;  4e ; 

c) The ratio of **3** : **4** are given in parentheses.

d) The ratio was determined by ^{1}H-NMR. See Ref. 8 .

but also an aromatic 1,2-diketone such as 1-phenyl-1,2-propanedione (Entry 5) reacted smoothly with aldehydes to afford the 2,3-dihydroxyketones in good yields with moderate diastereoselectivity. As shown in Entries 3, 4 and 5, it is noted that reactions of unsymmetrical 1,2-diketones with 3-phenylpropanal (**2a**) gave the products, which are formed by the reaction at the less hindered side of the 1,2-diketones, in high regioselectivity; the ratio of **3** to the other regioisomer **4** were determined to be 85 : 15, 96 : 4, and 93 : 7, respectively, by ^{1}H-NMR spectra. There is no report that exhibits such a high regioselectivity in the reaction of unsymmetrical 1,2-diketones except for mono-substituted glyoxals.[2,3] These results indicate that even small difference in steric hindrance of the substituents of 1,2-diketones plays an important part in the regioselectivity. Using aldehydes having functional groups such as olefinic or benzyloxyl group, the adducts were obtained in good yield (Entries 9 and 10), but the diastereoselectivity decreased in Entry 10. By this method, primary aldehydes reacted with 1,2-diketones to afford the adducts in good yield, but secondary and tertiary ones in poor yield. Aromatic aldehydes such as benzaldehyde give the self-coupling product predominantly rather than the aldol products .[10]

In this reaction, commercially available phenylglyoxal monohydrate **1k** as an α-keto aldehyde was directly used just after the azeotropic removal of water, giving the aldol product **3k** in 77% yield with the ratio of *anti* **3k** : *syn* **3k** = 63 : 37 (Eq. 2).



77% (*anti* **3k** : *syn* **3k** = 63 : 37)

A typical procedure is described as follows: Under an argon atmosphere, a SmI_2 THF solution (0.1 mol·dm^{-3}, 10 ml) was added to a THF (10 ml) solution of 2,3-butanedione (43.2 mg, 0.502 mmol), 3-phenylpropanal (105.1 mg, 0.783 mmol) and HMPA (184.1 mg, 1.027 mmol) at room temperature. After stirring for 30 min at that temperature, the reaction was quenched by hydrochloric acid (0.1 mol·dm^{-3}, 20 ml). Organic materials were extracted with diethyl ether three times, and combined organic layers were washed successively with brine, 4% $Na_2S_2O_3$ aq. and brine again, 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 : 1) to give the diastreomeric mixture of 3,4-dihydroxy-4-methyl-1-phenyl-5-hexanone (92.7 mg, 83% yield). Diastereomeric ratio and each configuration were determined by ^{1}H-NMR analysis.[8]

References

1) F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 543 (1965).

2) J. Ichikawa and T. Mukaiyama, *Chem. Lett.*, **1985**, 1009.

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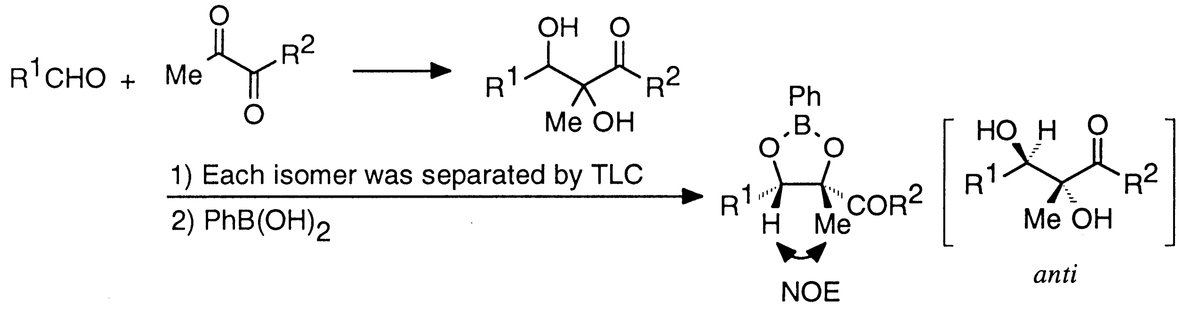
4) S. Takeuchi and Y. Ohgo, *Chem. Lett.*, **1988**, 403; S. Takeuchi, N. Miyoshi, K. Hirata, H. Hayashida, and Y. Ohgo, *Bull. Chem. Soc. Jpn.*, **65**, 2001 (1992). See also Ref. 5 .

5) SmI_2 has become a useful and unique reagent in organic synthesis since Kagan and his co-workers' pioneering work: J. L. Namy, P. Girard, and H. B. Kagan, *Nouv. J. Chim.*, **1**, 1 (1977). And for a recent review, see ; G. A. Molander, *Chem. Rev.*, **92**, 29 (1992).

6) J. Inanaga, M. Ishikawa, and M. Yamaguchi, *Chem. Lett.*, **1987**, 1485.

7) J. L. Namy, J. Souppe, and H. B. Kagan, *Tetrahedron Lett.*, **24**, 765 (1983).

8) Each diastereomeric ratio was determined by ^{1}H-NMR spectra of the mixture of *anti* **3**, *syn* **3**, and **4**. For Entries 1,3,4,6,8, and 10, each isomer9) was separated by TLC and the configuration was determined by ^{1}H-NMR(NOESY) spectrum of the corresponding phenyl boronate (Eq. 3). And others were inferred from analogy with the above results and Ref. 2.



(3)

9) ^{1}H-NMR spectral data of 3,4-dihydoxy-4-methyl-1-phenyl-5-hexanone are typically described as follows; *anti* **3a** ; δ=1.37(3H,s), 1.34-1.44(1H,m), 1.69-1.80(1H,m), 2.06(3H,s), 2.61-2.70(2H,m), 2.81-2.92(1H,m),3.55-3.64(1H,m), 3.98(1H,s), 7.14-7.30(5H,m).
syn **3a** ; δ=1.22(3H,s), 1.77-1.83(1H,m), 1.81(1H,d,J=10.2 Hz), 1.85-2.00(1H,m), 2.23(3H,s), 2.60-2.67(1H,m), 2.84-3.00(1H,m), 3.80(1H,dt,J=1.9,9.7 Hz), 4.02(1H,s), 7.20-7.45(5H,m).
The data of each isomer are well agreed with those of Ref. 2.

10) The reaction of benzaldehyde with 2,3-butanedione gave the products as follows; the aldol product (3,4-dihydroxy-3-methyl-4-phenyl-2-butanone) in 28% yield (28% based on SmI_2), the self-coupling one of the aldehyde (1,2-diphenyl-1,2-ethanediol) in 43% yield (32% based on SmI_2).

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