Synthesis of Hydroxy Ketones by Chemoselective Alkylation of Keto Aldehydes with Dialkylzincs Catalyzed by Amino Alcohol, Diamine, or Dilithium Salt of Piperazine

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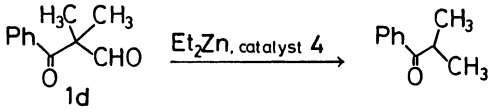
Synopsis. Hydroxy ketones were obtained in high yields by the chemoselective alkylation of formyl group of keto aldehydes with dialkylzincs in the presence of such catalysts as 2-dimethylaminoethanol, *N,N,N′,N′*-tetramethylethylenediamine, or dilithium salt of piperazine.

Chemoselective alkylation of aldehydes in the presence of ketones by organometallic reagents has attracted considerable attention.[1] Organolead,[1a] -lithium, -magnesium (in combination with organoaluminum),[1b] -lanthanoid (and Sc, Y, Nb, Ta),[1c] and -titanium reagents[1d] have been used for the above-mentioned reaction. However, most of the examples reported in these reports are intermolecular competitive experiments between aldehydes and ketones, and there are relatively few example of the chemoselective alkylation of keto aldehydes.

On the other hand, the addition of dialkylzincs to aldehydes without catalyst is very slow.[2] Mukaiyama et al., including one of us (K. S.), reported β-amino alcohol catalyzed addition of diethylzinc to benzaldehyde which affords 1-phenyl-1-propanol in 76%.[3]

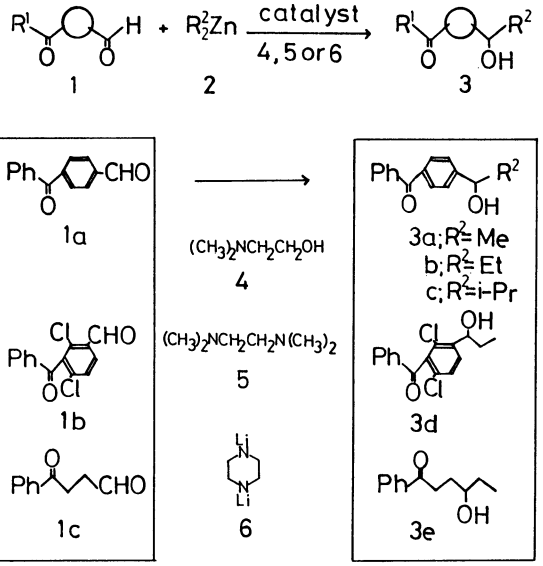
To establish the synthetic utility of the aminoalcohol-catalyzed addition of dialkylzincs to aldehydes, we report in this paper the chemoselective alkylation of the formyl group of keto aldehydes with dialkylzincs in the presence of such catalysts as 2-dimethylaminoethanol (**4**) or diamine (Scheme 1). When 4-benzoylbenzaldehyde (**1a**)[4] was treated with dimethyl-, diethyl-, or diisopropylzinc in the presence of 5—20 mol% of **4**, formyl group of **1a** was alkylated (methylation, ethylation, or isopropylation respectively) in chemoselective manner. The results are summarized in Table 1. Isolated yields of the corresponding hydroxy ketones (**3a—c**) were very high (93—100%) (Table 1, Entries 1—3). In a similar manner, chemoselective alkylation of 3-benzoyl-2,4-dichlorobenzaldehyde (**1b**) was performed. The yields of hydroxy ketone (**3d**) were quantitative regardless of the amount of catalyst (Entries 4 and 5). The reaction of 3-benzoylpropanal (**1c**, γ-keto aldehyde)[6] with Et_2Zn using **4** afforded γ-hydroxy ketone (**3e**) in 76% (Entry 8). *N,N,N′,N′*-tetramethylethylenediamine (**5**, TMEDA) and dilithium salt of piperazine (**6**)[5] were also found to be effective catalysts (Entries 6 and 7).

On the other hand, the reaction of 2-benzoyl-2-methylpropanal (**1d**, β-keto aldehyde)[7] with Et_2Zn using **4** as the catalyst (20 mol%) gave unexpected isopropyl phenyl ketone in 85% (Eq. 1). In addition,



(1)

intermolecular competitive ethylation of a mixture of benzaldehyde and acetophenone using **4** (10 mol%) afforded 1-phenyl-1-propanol (75%)(as a result of the ethylation of benzaldehyde), and acetophenone was recovered (70%).



Scheme 1.

Experimental

All reactions were carried out under an argon atmosphere. Toluene was distilled from lithium aluminum hydride. 4-Benzoylbenzaldehyde (**1a**),[4] 3-benzoylpropanal (**1c**),[6] and 2-benzoyl-2-methylpropanal (**1d**)[7] were prepared according

Table 1. Synthesis of Hydroxy Ketones (**3**) from Keto Aldehydes (**1**)

Entry[a]	1	R^2	Catalyst	Mole ratio[b]	3	Yield/%
1	**a**	Me	**4**	A	**a**	100
2	**a**	Et	**4**	B	**b**	93
3	**a**	*i*-Pr	**4**	C	**c**	100
4	**b**	Et	**4**	B	**d**	100
5	**b**	Et	**4**	D	**d**	100
6	**b**	Et	**5**	B	**d**	100
7	**b**	Et	**6**	B	**d**	77
8[c]	**c**	Et	**4**	E	**e**	76

a) Unless otherwise noted, reactions were run at room temperature. b) Molar ratio of keto aldehyde (**1**):dialkylzinc (**2**):catalyst. A=1.0:4.0:0.2. B=1.0:2.2:0.05. C=1.0:2.2:0.2. D=1.0:2.2:1.0. E=1.0:4.0:0.1. c) Reaction was run at 0 °C.

to a method described in the literature. 2,4-Dichloro-3-benzoylbenzaldehyde and diethylzinc are commercially available. Diisopropylzinc was prepared according a method from the literature and was purified by distillation.[8] ^{1}H NMR spectra were taken on a JEOL JNM PMX-60 (TMS as the internal reference). The IR spectra were recorded on a Hitachi 260-10 spectrometer. Measurement of mass spectra were carried out on a Hitachi RMU7M spectrometer.

Typical Procedure for Chemoselective Alkylation of Keto Aldehydes with Dialkylzincs Using 2-Dimethylaminoethanol (Table 1, Entry 2): A toluene solution of 2-dimethylaminoethanol (**4**, 0.05 M,† 0.025 mmol) was added to a toluene solution (0.5 ml) of 4- benzoylbenzaldehyde (**1a**, 0.106 g, 0.50 mmol) at 0 °C. After 15 min of stirring, diethylzinc (1.1 ml, 1 M, in hexane solution) was added dropwise. The resulting mixture was stirred at room temperature for 14 h and quenched with 1 M HCl (3 ml), the organic layer was separated, and aqueous layer was extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, then evaporated under reduced pressure. The residue was purified by silica gel TLC [$CHCl_3$: MeOH=50 : 1 v/v as eluent]. 4-(1-Hydroxypropyl)benzophenone (**3b**) was obtained in 93% yield (0.113 g, 0.47 mmol); ^{1}H NMR ($CDCl_3$) δ=0.73—1.16 (t, 3H), 1.50—2.05 (m, 2H), 2.96 (s, 1H), 3.46—4.74 (t, 3H), and 7.12—7.91 (m, 9H); IR (neat) 3430, 2970, and 1660 cm^{-1}; Found: *m/z* 240.1148. Calcd for $C_{16}H_{16}O_2$: M, 240.1151.

According to a similar procedure as that described above, the following hydroxy ketone (**3**) were synthesized from the corresponding **1** and **2** using **4** or **5** as the catalyst.

4-(1-Hydroxyethyl)benzophenone (3a, Table 1, Entry 1): Yield 100%; ^{1}H NMR ($CDCl_3$) δ=1.40—1.67 (d, 3H), 2.76—3.17 (broad, 1H), 4.67—5.01 (m, 1H), and 7.17—7.90 (m, 9H); IR (neat) 3420, 2975, and 1660 cm^{-1}; Found: *m/z* 226.0994. Calcd for $C_{15}H_{14}O_2$: M, 226.0994.

4-(1-Hydroxy-2-methylpropyl)benzophenone (3c, Table 1, Entry 3): Yield 100%; ^{1}H NMR ($CDCl_3$) δ= 0.57—1.30 (m, 6H), 1.67—2.30 (m, 1H), 2.78 (s, 1H), 4.20—4.67 (m, 1H), and 7.03—8.00 (m, 9H); IR (neat) 3450, 2960, and 1650 cm^{-1}; Found: *m/z* 254.1301. Calcd for $C_{17}H_{18}O_2$: M, 254.1307.

2,6-Dichloro-3-(1-hydroxypropyl)benzophenone (3d, Table 1, Entries 4, 5, 6, and 7): Yield 77—100%; ^{1}H NMR ($CDCl_3$) δ=0.83—1.20 (t, 3H), 1.47—2.23 (m, 3H), 4.87—5.33 (m, 1H), and 7.24—8.93 (m, 7H); IR (neat) 3370, 2920, and 1660 cm^{-1}; Found: *m/z* 308.0378. Calcd for $C_{16}H_{14}O_2Cl_2$; M, 308.0372.

† 1 M=1 mol dm^{-3}.

Dilithium salt of piperazine (**6**) was in situ prepared by the treatment of piperazine with 2 equiv of butyllithium (Entry 7).

4-Hydroxy-1-phenyl-1-hexanone (3e, Table 1, Entry 8): Yield 76%; ^{1}H NMR ($CDCl_3$) δ=0.80—1.17 (m, 3H), 1.30—2.13 (m, 5H), 3.00—3.33 (t, 2H), 3.33—3.77 (m, 1H), and 7.20—8.13 (m, 5H); IR (neat) 3450, 2970, and 1685 cm^{-1}; Found: *m/z* 192.1143. Calcd for $C_{12}H_{16}O_2$: M, 192.1151.

Reaction of 1d with Diethylzinc Using 4: The reaction of **1d** (0.174 g, 0.99 mmol) under the same reaction conditions using Et_2Zn instead of diisopropylzinc (Table 1, Entry 3) for 56 h afforded 0.125 g of isopropyl phenyl ketone in 85% yield.

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