$Sm/BiCl_3$ System Mediated Reformatsky Type Reactions of α-Bromoacetophenone with Aldehydes in THF-H_2O Solvent

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In the presence of samarium-bismuth(III) chloride, intermolecular aldol type reactions of α-bromoacetophenone with various aldehydes in tetrahydrofuran-water mixed solvent afford β-hydroxy ketones in moderate to good yields under mild and neutral conditions.

Keywords samarium, bismuth(III) chloride, Reformatsky-type reaction, aldehydes and α-bromoacetophenone

The classical Reformatsky type reaction is one of the most important reactions to prepare the β-hydroxy carbonyl compounds. Metallic zinc plays an important role in the reactions. By increasing the reactivity of the zinc, or by application of various other metals or metal salts, more and more progresses have been achieved.[1] For example, Nozaki and co-workers reported the Reformatsky type reactions of α-halogeno ketones with carbonyl compounds promoted by the coupling metallic zinc and Et_2AlCl or $Bu_3SnAlEt_2$.[2] Reaction of metallic tin with α-halogeno ketones gave the tin(II) enolates which gave β-hydroxy ketones in good yields when treated with carbonyl compounds.[3] Samarium(II) diiodide was also used to promote the intermolecular or intramolecular aldol type reactions of α-halogeno ketones with carbonyl compounds.[4] Recently, some Reformatsky type reactions were carried out in aqueous media using zinc powder,[5] tin-aluminum couple.[6] It is well known that the organic reactions in aqueous media offer a number of advantages over the conventional organometallic reactions in organic solvents.[7] There is the practical convenience, and no need to use absolute anhydrous organic solvents. Since $Sm/BiCl_3$ bimetallic system is an efficient system in the reduction of diselenides or disulfides,[8] in order to expand its uses and continue our research in developing new synthetic application of Sm/MCl_n system,[9] here we wish to report an efficient method for the Reformatsky-type reaction promoted by $Sm/BiCl_3$ bimetallic system in tetrahydrofuran-water mixed solvent (as shown in Scheme 1).

Scheme 1

$$\underset{\mathbf{1}}{PhCOCH_2Br} + \underset{\mathbf{2}}{RCHO} \xrightarrow[THF\text{-}H_2O]{Sm/BiCl_3} \underset{\mathbf{3}}{PhCOCH_2\overset{OH}{\overset{|}{C}}HR}$$

The reactions generally proceeded smoothly with both aromatic and aliphatic aldehydes. The better yields of the products demonstrate the efficiency of this new method. The Table summarizes our results on the coupling of aldehydes and α-bromoacetophenone. When the reactions proceeded at room temperature, the yield was much lower than that at 50 ℃ (Entry j). While the temperature was raised to reflux, the yield was just the same as that at 50 ℃ (Entry k). By comparison of kinds of solvents, the most appropriate ratio of THF to H_2O was 10∶1. The reaction carried out smoothly with the aldehydes containing reactive groups such as halo-

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gen, alkoxy group (Entry b and c). Interestingly, when the nitro-substituted benzaldehyde (Entry e) reacted with α-bromoacetophenone, the corresponding β-hydroxy ketone was obtained and nitro group was not reduced. When acetophenone was used to react with α-bromoacetophenone under this condition, the corresponding β-hydroxy ketone was too little to be isolated (Entry n).

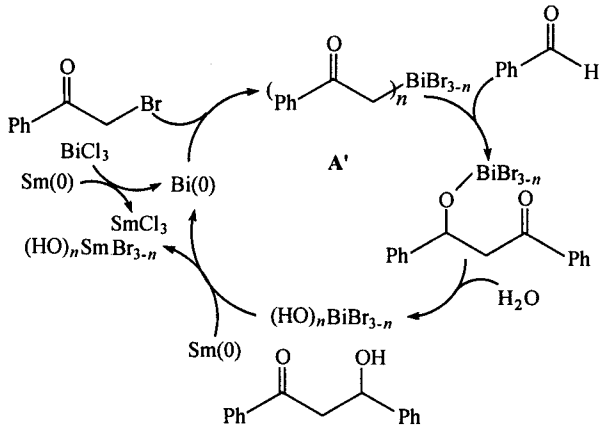
Although the reaction mechanism is not clear yet, we think it may involve acylbismuth formed through the addition of α-bromoacetophenone to Bi(0) generated by the reduction of $BiCl_3$ with Sm metal (as shown in Scheme 2).

Table Reaction of aldehydes with α-bromoacetophenone mediated by Sm/$BiCl_3$ system

Entry	Aldehyde	Solvent	T/t (℃/h)	Yield[a] (%)
a	C_6H_5CHO	THF/H_2O 10/1	50/6	75
b	*p*-ClC_6H_4CHO	THF/H_2O 10/1	50/6	81
c	*p*-$CH_3OC_6H_4CHO$	THF/H_2O 10/1	50/6	69
d	*p*-$CH_3C_6H_4CHO$	THF/H_2O 10/1	50/6	55
e	*m*-$NO_2C_6H_4CHO$	THF/H_2O 10/1	50/6	65
f	C_3H_7CHO	THF/H_2O 10/1	50/6	71
g	C_4H_9CHO	THF/H_2O 10/1	50/6	73
h	$C_6H_{13}CHO$	THF/H_2O 10/1	50/6	65
i	$C_6H_5CH=CHCHO$	THF/H_2O 10/1	50/6	69
j	*p*-ClC_6H_4CHO	THF/H_2O 10/1	25/6	52
k	*p*-ClC_6H_4CHO	THF/H_2O 10/1	67/6	78
l	*p*-ClC_6H_4CHO	THF	50/6	78
m	*p*-ClC_6H_4CHO	THF/H_2O 10/2	50/6	75
n	$C_6H_5COCH_3$	THF/H_2O 10/1	50/6	—

[a] Isolated yields based on aldehydes.

Scheme 2



In summary, we provide an efficient Reformatsky-type reaction of aldehydes and α-bromoacetophenone mediated by Sm/$BiCl_3$ bimetallic system in THF-H_2O mixed solvent. A number of β-hydroxy ketones were synthesized in satisfactory yields. The notable advantages of this Reformatsky type reaction are mild and neutral conditions, simple operation, non-toxicity and higher yields.

Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points were uncorrected. Infrared spectra were recorded on a Bruker vector 22 spectrometer in KBr or film with absorption in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC-80 spectrometer as $CDCl_3$ solutions. J values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane.

General procedure of preparation of 3-hydroxyl-1,3-diphenylpropane-1-one (**3a**)

To a mixture of samarium powder (2 mmol) and bismuth(III) chloride (1 mmol) was added THF (10 mL) and water (1 mL), benzaldehyde (1 mmol), α-bromoacetophenone (1.2 mmol) were added under a nitrogen atmosphere at room temperature. Then the mixture was stirred and heated to the appropriate temperature.

After the reaction was completed (monitored by TLC), the reaction was quenched with a little water. The mixture was extracted with diethyl ether (3 × 15 mL). The combined extracts were washed with saturated brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative thick layer chromatography using ethyl acetate and cyclohexane (1:3) as eluant.

3a m.p. 44—44 ℃ (lit.[10] 44—46 ℃); ^{1}H NMR ($CDCl_3$) δ: 7.95—7.10 (m, 10H), 5.35—5.15 (m, 1H), 3.45 (br, 1H), 3.30 (d, J = 6.0 Hz, 2H); IR (KBr) ν: 3490, 3050, 1680, 1600, 1580, 1450, 1330, 1210, 1010, 770 cm^{-1}.

3b m.p. 95—96 ℃ (lit.[10] 96—96.5 ℃); ^{1}H NMR ($CDCl_3$) δ: 8.00—7.10 (m, 9H), 5.35—5.10 (m, 1H), 3.75 (br, 1H), 3.30 (d, J = 6.0 Hz, 2 H); IR (KBr) ν: 3460, 3060, 2985, 1670, 1600, 1500, 1450, 1395, 1280, 1210, 1020, 830, 750, 690 cm^{-1}.

3c oil (lit.[10]); ^{1}H NMR ($CDCl_3$) δ: 8.00—7.00 (m, 9 H), 5.25—4.90 (m, 1 H), 3.80 (s, 3H), 3.40 (br, 1H), 3.35 (d, J = 5.7 Hz, 2H); IR (film): 3480, 3030, 1670, 1590, 1510, 1445, 1330, 1240, 1010, 760 cm^{-1}.

3d m.p. 46—47 ℃ (lit.[10] 47—48 ℃); ^{1}H NMR ($CDCl_3$) δ: 7.95—7.05 (m, 9H), 5.40—5.10 (m, 1H), 3.65 (br, 1H), 3.30 (d, J = 5.8 Hz, 2H), 2.30 (s, 3H); IR (KBr) ν: 3460, 3050, 1675, 1600, 1580, 1440, 1350, 1210, 1015, 755 cm^{-1}.

3e oil (lit.[11]); ^{1}H NMR ($CDCl_3$) δ: 8.20—7.25 (m, 9H), 5.35—5.15 (m, 1H), 3.60 (br, 1H), 3.40 (d, J = 6.0 Hz, 2H); IR (film) ν: 3500, 1670, 1595, 1510, 1455, 1440, 1350, 1200, 1080, 880, 840, 760, 690 cm^{-1}.

3f oil (lit.[12]); ^{1}H NMR ($CDCl_3$) δ: 7.80—7.35 (m, 5H), 4.05—3.90 (m, 1H), 3.05 (br, 1H), 2.40 (d, J = 5.8 Hz, 2H), 1.30—0.85 (m, 7H); IR (film) ν: 3490, 2980, 1670, 1620, 1600, 1460, 1210, 750, 690 cm^{-1}.

3g oil (lit.[13]); ^{1}H NMR ($CDCl_3$) δ: 7.75—7.35 (m, 5H), 4.10—3.85 (m, 1H), 2.95 (br, 1H), 2.40 (d, J = 6.0 Hz, 2H), 1.40—0.80 (m, 9H); IR (film) ν: 3440, 2980, 1705, 1620, 1580, 1450, 1220, 770, 680 cm^{-1}.

3h oil (lit.[11]); ^{1}H NMR ($CDCl_3$) δ: 7.80—7.30 (m, 5H), 4.15—3.85 (m, 1H), 3.00 (br, 1H), 2.50 (d, J = 6.0 Hz, 2H), 1.40—0.80 (m, 13H); IR (film) ν: 3440, 2980, 1705, 1620, 1580, 1450, 1220, 770, 680 cm^{-1}.

3i m.p. 50—51 ℃ (lit.[14] 51—53 ℃); ^{1}H NMR ($CDCl_3$) δ: 7.90—7.15 (m, 10 H), 6.65—5.80 (m, 2 H), 5.05—4.65 (m, 1H), 3.30 (br, 1H), 2.90 (d, J = 5.8 Hz, 2H); IR (KBr) ν: 3460, 2975, 1660, 1605, 1580, 1440, 1250, 770 cm^{-1}.

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