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Indium-Induced Reaction of Phenacyl Iodide. Deiodinative Dimerization to β,γ-Epoxy Ketone and Aldol Condensation with Aldehydes

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Synopsis. The reaction of phenacyl iodide with indium metal gave 3,4-epoxy-1,3-diphenyl-1-butanone which, on treatment with silica gel, gave 2,4-diphenylfuran and 2,4-diphenyl-4-oxobutanal. Metallic indium as well as indium(I) iodide were found to mediate the aldol condensation between α-halo ketone and aldehyde.

We have recently reported that activated halides such as allylic halides[1)] and α-iodoacetate[2)] react with metallic indium to form organoindium compounds and these reagents have been proved to be useful in organic synthesis. In order to extend the synthetic utility of organoindium reagents, we have studied the generation and reaction of indium enolates of ketones. We describe here the reaction of phenacyl iodide with indium metal which leads to a β,γ-epoxy ketone. The same reaction in the presence of an aldehyde gave aldol condensation products. The aldol reaction using indium(I) iodide is also described.

An exothermic reaction of phenacyl iodide and indium powder took place in DMF at room temperature. Aqueous workup and distillation gave 3,4-epoxy-1,3-diphenyl-1-butanone (**1**) (57% yield) together with small amounts (<3%) of acetophenone and 1,2-dibenzoylethane. The epoxy ketone **1** is acid-labile; by adsorption on silica gel, **1** was completely converted to 2,4-diphenylfuran (**2**) and 2,4-diphenyl-4-oxobutanal (**3**), in 40 and 48% yields, respectively. The above transformations are illustrated in Scheme 1, in which the indium enolate **4** is postulated as an intermediate.

The syntheses of 2,4-disubstituted furans from the reaction of α-halo ketones have been performed by using magnesium,[3)] zinc,[4)] tetracarbonylnickel(0),[5)] or copper(I) chloride.[6)] Yoshisato and Tsutsumi have reported the synthesis of β,γ-epoxy ketone from aliphatic α-bromo ketone and realized its thermal transformation to 2,4-dialkylfuran.[5b)] However, the compound **1** has never been obtained so far by the reactions of the metal enolates derived from phenacyl bromide,[5a,6,7)] probably owing to its instability.

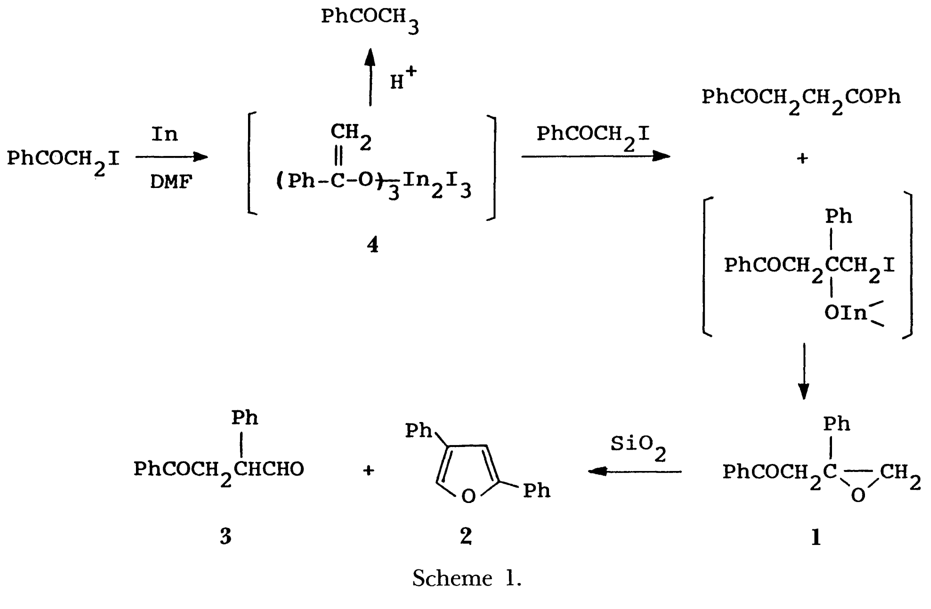
When the above reaction of phenacyl iodide with indium was conducted in the presence of an aldehyde, the aldol condensation proceeded; i.e., with benzaldehyde were formed β-hydroxy ketone **5** and chalcone (**6**) in 53 and 17% yields, respectively. Octanal gave similar results (Eq. 1).

$$\mathrm{PhCOCH_2I + RCHO \xrightarrow[\text{DMF}]{\text{In}}}$$

$$\mathrm{PhCOCH_2CH(OH)R + PhCOCH{=}CHR} \qquad (1)$$

$$\begin{array}{ll} \mathbf{5}\ (\mathrm{R{=}Ph})\ 53\% & \mathbf{6}\ (\mathrm{R{=}Ph})\ 17\% \\ \mathbf{7}\ (\mathrm{R{=}heptyl})\ 43\% & \mathbf{8}\ (\mathrm{R{=}heptyl})\ 17\% \end{array}$$

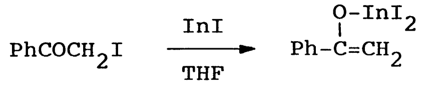
It has previously been shown that indium(I) iodide can be used for oxidative addition to allylic halides and α-iodoacetate in place of metallic indium.[8)] Indium(I) iodide has now been found to be effective also for the formation of the indium enolate from phenacyl iodide. Thus, refluxing of a mixture of phenacyl iodide and indium(I) iodide in THF for 12 h and aqueous workup of the reaction mixture gave



Scheme 1.

Table 1. Indium(I) Iodide-Induced Condensation of α-Bromo Ketones with Aldehydes

α-Bromo Ketone	Aldehyde	Product	Yield/%
$PhCOCH_2Br$	PhCHO	PhCOCH=CHPh (**6**)	74
$PhCOCH_2Br$	p-ClC_6H_4CHO	$PhCOCH{=}CHC_6H_4Cl$-p (**10**)	75
$PhCOCH_2Br$	$CH_3(CH_2)_6CHO$	$PhCOCH{=}CH(CH_2)_6CH_3$ (**8**)	77
$PhCOCH_2Br$	PhCH=CHCHO	PhCOCH=CHCH=CHPh (**11**)	53
p-$BrC_6H_4COCH_2Br$	p-ClC_6H_4CHO	p-$BrC_6H_4COCH{=}CHC_6H_4Cl$-$p$ (**12**)	63
CH_3COCH_2Br	PhCHO	$CH_3COCH{=}CHPh$ (**13**)	40
CH_3COCH_2Br	$CH_3(CH_2)_6CHO$	$CH_3COCH{=}CH(CH_2)_6CH_3$ (**14**)	52



$$PhCOCH_2I \xrightarrow[THF]{InI} Ph\text{-}\overset{O\text{-}InI_2}{C}{=}CH_2 \qquad (2)$$

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acetophenone in 75% yield together with a trace amount of 1,2-dibenzoylethane. This supports the in situ formation of the indium enolate **9** (Eq. 2). Phenacyl bromide was equally reactive to the iodide. When the reaction of α-bromo ketones and indium(I) iodide was carried out with aldehydes, α,β-unsaturated ketones were obtained. Table 1 summarizes the results. Both aromatic and aliphatic α-bromo ketones gave moderate yields of α,β-unsaturated ketones. The corresponding β-hydroxy ketones were not found in the reaction mixtures owing to a facile dehydration under the reaction conditions employed.

Experimental

General. Melting points were determined with a Mitamura Riken micro melting point apparatus and are uncorrected. IR spectra were taken with a JASCO A-102 spectrophotometer. Mass spectra (MS) were recorded with a Hitachi M-2000 instrument at 70 eV. ^{1}H NMR spectra were obtained with a Hitachi R-90 (90 HMz) spectrometer. ^{13}C NMR spectra were obtained with a Varian XL-200 (50.3 MHz) spectrometer. Elemental analyses were performed at Elemental Analysis Center of Kyoto University. Indium powder (99.99%, stabilized by 0.5% MgO) was obtained from Nacalai Tesque Co., Ltd. THF (tetrahydrofuran) and DMF (*N,N*-dimethylformamide) were distilled from lithium aluminum hydride and calcium hydride, respectively. All reactions were conducted under argon.

Reaction of Phenacyl Iodide with Indium. To a suspension of indium powder (114 mg, 1 mmol) in DMF (1 cm^3) was added phenacyl iodide (492 mg, 2 mmol) at room temperature. An exothermic reaction started immediately. The mixture was stirred at room temperature for 100 min. Water was added and the products were extracted with ether. The extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent left an oil which was distilled (Kugelrohr) to give acetophenone [bp 100 °C/1 Torr (1 Torr=133.322 Pa), bath temperature] (8 mg, 3%) and **1** (bp 190 °C/1 Torr, bath temperatures) (136 mg, 57%). The latter contained a trace amount of 1,2-dibenzoylethane which was crystallized and filtered (mp 142 °C, lit,[5a] mp 145 °C).

3,4-Epoxy-1,3-diphenyl-1-butanote (1). Colorless oil; IR (neat) 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.97 (1H, d, J=5 Hz, OCH_2), 3.10 (1H, d, J=5 Hz, OCH_2), 3.58 (1H, d, J=17 Hz, $PhCOC\underline{H}_2$), 3.77 (1H, d, J=17 Hz, $PhCOC\underline{H}_2$), 7.36 (8H, m, aromatic), and 7.95 (2H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=45.3 (t), 55.3 (t), 57.1 (s), 125.8 (d), 127.8 (d), 128.3 (d), 128.4 (d), 128.6 (d), 133.4 (d), 136.8 (s), 139.6 (s), and 196.8 (s); MS m/z 238 (M^+); Found: C, 80.56; H, 5.98%. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92%.

Treatment of 1 with Silica Gel. A solution of **1** (114 mg, 0.48 mmol) in dichloromethane was adsorbed on a silica-gel column. After 1.5 h at room temperature, the column was eluted with acetone. The eluate showed two spots on a thin-layer chromatogram, which were separated by column chromatography on silica gel (hexane–dichloromethane gradient) to give **2** (42 mg, 40%) and **3** (55 mg, 48%).

2,4-Diphenylfuran (2). Colorless crystals; mp 111 °C (lit,[5a] mp 111 °C); ^{1}H NMR ($CDCl_3$) δ=6.95 (1H, d, J=1 Hz, H^3), 7.38 (8H, m, aromatic), 7.70 (2H, m, aromatic), and 7.75 (1H, d, J=1 Hz, H^5).

2,4-Diphenyl-4-oxobutanal (3). Colorless oil; IR (neat) 1722 (aldehyde C=O) and 1680 cm^{-1} (ketone C=O); ^{1}H NMR ($CDCl_3$) δ=3.30 (1H, dd, J=18, 5 Hz, CH_2), 3.93 (1H, dd, J=18, 8 Hz, CH_2), 4.41 (1H, dd, J=8, 5 Hz, $C\underline{H}CHO$), 7.31 (8H, m, aromatic), 7.98 (2H, m, aromatic), and 9.81 (1H, bs, CHO); ^{13}C NMR ($CDCl_3$) δ=39.3 (t), 53.5 (d), 127.8 (d), 128.0 (d), 128.5 (d), 129.0 (d), 129.2 (d), 133.2 (d), 135.3 (s), 136.3 (s), 197.2 (s), and 198.9 (d); MS m/z 238 (M^+); Found: C, 80.39; H, 5.72%. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92%.

Indium-Induced Reaction of Phenacyl Iodide with Aldehydes. To a mixture of indium powder (114 mg, 1 mmol) and benzaldehyde (159 mg, 1.5 mmol) in DMF (1 cm^3) was added phenacyl iodide (246 mg, 1 mmol) at room temperature. After a reaction started (exothermic), the mixture was cooled to 0 °C and stirred for 70 min. Water was added and the products were extracted with ether. Extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (eluent: CH_2Cl_2) to give **5** (120 mg, 53%) and **6** (35 mg, 17%). The reaction with octanal was similarly carried out.

3-Hydroxy-1,3-diphenyl-1-propanone (5). Colorless oil; (lit,[9] mp 50—50.5 °C); ^{1}H NMR ($CDCl_3$) δ=3.35 (2H, d, J=6 Hz, CH_2), 3.40 (1H, bs, OH), 5.32 (1H, t, J=6 Hz, CH), 7.38 (8H, m, aromatic), and 7.90 (2H, m, aromatic).

Chalcone (6). Yellow crystals; mp 55 °C (lit,[10] mp 56—58 °C); ^{1}H NMR ($CDCl_3$) δ=7.50 (10H, m, =CH- and aromatic) and 7.97 (2H, m, aromatic).

3-Hydroxy-1-phenyl-1-decanone (7). Colorless crystals; mp 48 °C; IR (KBr) 3420 (OH) and 1672 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, bt, J=6 Hz, Me), 1.30 (12H, m, CH_2), 2.90 (1H, bs, OH), 3.08 (1H, dd, J=18, 7 Hz, $COCH_2$), 3.13 (1H, dd, J=18, 4 Hz, $COCH_2$), 4.20 (1H, m, $C\underline{H}(OH)$), 7.53 (3H, m, aromatic), and 7.97 (2H, m, aromatic); MS m/z 230 ($M-H_2O$); Found: C, 77.02; H, 9.95%. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74%.

1-Phenyl-2-decen-1-one (8). Colorless oil; IR (neat) 1668 and 1620 cm^{-1} (CH=CH-C=O); ^{1}H NMR ($CDCl_3$) δ=0.88 (3H, bt, J=6 Hz, Me), 1.30 (10H, m, CH_2), 2.32 (2H, bq, J=6 Hz, CH_2), 6.87 (1H, d, J=15 Hz, =CH-), 7.00 (1H, dt, J=15, 6 Hz, =CH-), 7.50 (3H, m, aromatic), and 7,93 (2H, m, aromatic); MS m/z 230 (M^+); Found: C, 82.70; H, 9.69%. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63%.

Reaction of Phenacyl Iodide with Indium(I) Iodide. A mixture of phenacyl iodide (123 mg, 0.5 mmol) and indium(I) iodide[11] (130 mg, 0.54 mmol) in THF (5 cm^3) was heated at reflux for 12 h. Hydrochloric acid (3%) was added and the products were extracted with dichloromethane. The extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (eluent: CH_2Cl_2) to give acetophenone (45 mg, 75%) and a trace amount of 1,2-dibenzoylethane (ca. 3 mg).

Indium(I) Iodide-Induced Reaction of α-Bromo Ketones with Aldehydes. General Procedure: A mixture of α-bromo ketone (0.8 mmol), aldehyde (0.5 mmol), and indium(I) iodide (0.8 mmol) was refluxed in THF (5 cm^3) for 12—17 h. Diluted hydrochloric acid (3%) was added and the product was extracted with dichloromethane. The extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (eluent: CH_2Cl_2) to give α,β-unsaturated ketone.

3-(4-Chlorophenyl)-1-phenyl-2-propen-1-one (10). Yellow crystals; mp 112 °C (lit,[10] mp 114—115 °C); ^{1}H NMR ($CDCl_3$) δ=7.55 (9H, m, =CH- and aromatic) and 7.99 (2H, m, aromatic).

1,5-Diphenyl-2,4-pentadien-1-one (11). Yellow crystals; mp 100 °C (lit,[12] mp 102—103 °C); ^{1}H NMR ($CDCl_3$) δ=6.9—7.7 (12H, m, =CH- and aromatic) and 7.95 (2H, m, aromatic).

1-(4-Bromophenyl)-3-(4-chlorophenyl)-2-propen-1-one (12). Yellow crystals; mp 161 °C (lit,[13] mp 167—168 °C); ^{1}H NMR ($CDCl_3$) δ=7.3—7.9 (m, 10H, =CH- and aromatic).

4-Phenyl-3-buten-2-one (13). Yellow crystals; mp 40 °C (lit,[14] mp 41.5—42 °C); ^{1}H NMR ($CDCl_3$) δ=2.37 (3H, s, Me), 6.73 (1H, d, J=16 Hz, =CH-), and 7.45 (6H, m, =CH- and Ph).

3-Undecen-2-one (14).[15] Colorless oil; ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, bt, J=6 Hz, Me), 1.30 (10H, m, CH_2), 2.23 (5H, m, CH_2 and COMe), 6.07 (1H, d, J=16 Hz, =CH-), and 6.80 (1H, dt, J=16, 7 Hz, =CH-).

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