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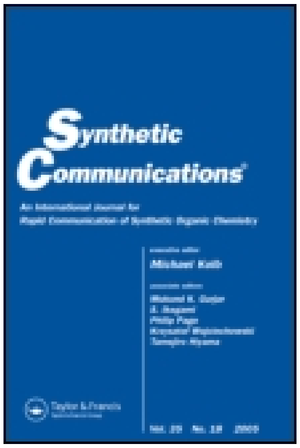

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Indium Trichloride Catalyzes Aldol-Condensations of Aldehydes and Ketones

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Indium Trichloride Catalyzes Aldol-Condensations of Aldehydes and Ketones

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ABSTRACT

$InCl_3 \cdot 4H_2O$ catalyzes the cross-aldol condensation of different ketones with various aldehydes to give α,β-unsaturated carbonyl compounds in good to excellent yields.

α,β-Unsaturated carbonyl compounds play a very important role in organic synthesis.[1] Many methods for synthesis of the compounds have been reported.[2] Among them, the most typical method is aldol-condensation. Aldol-condensation reactions were usually carried out in the presence of strong acids or bases.[3] In these cases, many side reactions occurred. The condensation reactions were also performed in neutral

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conditions using some metal ions as catalyst to reduce side reactions. However, there were also some disadvantages in these methods because of using different complexes of metal ions, such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) with different ligands.[4]

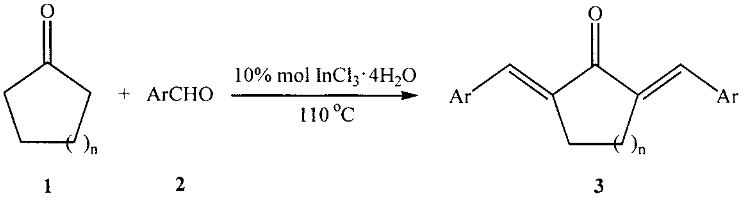
The uses of $Ti(OR)_4$[5] and $TiCl_3(SO_3CF_3)$[6] have been reported for cross condensation of aldehydes and ketones. However, they can be hydrolyzed in the presence of water, which may result in the aldol-condensation reaction.[7] $TiCl_4$ was used to promote the self-condensation of ketones and aliphatic aldehydes rather than the cross-aldol condensation.[8] Bis(*p*-Ethoxyphenyl) telluroxide (BMPTO) has been used as catalyst for cross condensation of cyclohexanone and cyclopentanone with aromatic aldehydes under microwave irradiation.[9] With this method, in most cases, the obtained yields for cross-condensation of cyclohexanone are not very good.

$RuCl_3$ has also been reported to be an excellent catalyst, which can promote cross-condensation or self-condensation reaction of aldehydes and ketones.[10] However, the disadvantage is that $RuCl_3$ is expensive.

Owing to the importance of aldol-condensation reactions in organic chemistry and some disadvantages in the reported methods, it is significant to exploit new and efficient catalysts for aldol-condensation reactions. Herein we report an efficient procedure for cross and self-condensation reaction of different aldehydes and ketones including cycloalkanones. In our procedure hydrous indium trichloride ($InCl_3 \cdot 4H_2O$) can effectively catalyze both cross and self-condensation reactions of different aldehydes and ketones including cycloalkanones.

The cross-condensations of cyclopentanone and cyclohexanone with various aromatic aldehydes were carried out as well in the presence of 0.1 molar equivalents of $InCl_3 \cdot 4H_2O$ in sealed tube at 110°C (Sch. 1). As shown in Table 1, the reactions were finished within 6–24 h and yields were excellent. Di-aldol products were only obtained without products of mono-aldol and self-condensation of cycloalkanones under these conditions. In other experiments, we have found that, if these reactions were carried out in open vessel at 110°C in the absence of solvent or under reflux conditions in solvents such as benzene, toluene, acetonitrile, and DME, etc, yields were below 50%. In comparison, this reaction were carried in sealed tube at 110°C but in the absence of $InCl_3 \cdot 4H_2O$ and solvent, one tenth of the yields in Table 1 were only obtained in the same reaction time.

As shown in Table 2, enolizable aromatic ketones react with non-enolizable aromatic aldehydes to afford (*E*)-α,β-unsaturated ketones (**3i–j**). Enolizable aliphatic aldehydes such as butyraldehyde undergo self-condensation to the corresponding α,β-unsaturated aldehyde (**3k**)



3a	n=2	Ar=C_6H_5	**3e**	n=2	Ar=*p*-$CH_3OC_6H_4CHO$
3b	n=2	Ar=*p*-ClC_6H_4CHO	**3f**	n=1	Ar=C_6H_5
3c	n=2	Ar=*p*-$O_2NC_6H_4CHO$	**3g**	n=1	Ar=*p*-$O_2NC_6H_4CHO$
3d	n=2	Ar=*p*-$CH_3C_6H_4CHO$	**3h**	n=1	Ar=*p*-$CH_3OC_6H_4CHO$

Scheme 1.

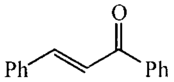
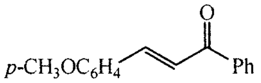
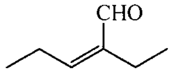
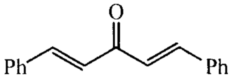
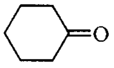
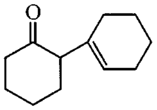
Table 1. Cross-aldol condensation reaction of cycloalkanones with aromatic aldehydes in the presence of 10% molar equivalents of $InCl_3 \cdot 4H_2O$ in sealed tube at 110°C.

Entry[a]	Reaction Time (h)	Yield[b] (%)
3a	6	95(2)[c]
3b	10	93
3c	24	93
3d	4	94
3e	10	90
3f	10	89
3g	24	91
3h	12	94

[a] All compounds were confirmed by ^{1}H NMR and IR.
[b] Isolated yield.
[c] Number in parenthesis refers to the yield in the absence of any catalyst.

under the sealed and free solvent conditions at 110°C. Cross-condensation reaction of acetone and benzaldehyde afford 1:2 (*E*, *E*)-condensation product (**3l**) when a mole ratio of benzaldehyde and acetone is up to 2:1. Cycloalkanones such as cyclohexanone, which are less reactive, afford the 1:1 self-condensation product (**3m**).

Table 2. Aldol-condensation between aliphatic and aromatic aldehydes or ketones in the presence of 10% molar equivalents of $InCl_3 \cdot 4H_2O$ in sealed tube at 110°C.

Entry[a]	Substrate	Product	Reaction time (h)	Yield[b] %
3i	$PhCOCH_3$ $+ PhCHO$		72	92
3j	$PhCOCH_3$ $+ p\text{-}CH_3OC_6H_4CHO$		72	94
3k	$CH_3CH_2CH_2CHO$		4	90
3l	CH_3COCH_3 $+ PhCHO$		16	88
3m			48	85

[a]All compounds were confirmed by ^{1}H NMR and IR.
[b]Isolated yield.

In a word, $InCl_3 \cdot 4H_2O$ is an efficient catalyst for aldol-condensation. It proceeds to broaden the scope of the condensation reaction in our group.

EXPERIMENTAL SECTION

M.p.s are uncorrected. ^{1}H NMR spectra were recorded on Varian Mercury 200 spectrometer, using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. IR spectra were recorded on a Nicolet instrument corporation's IR-510P spectrometer.

Typical procedure for the synthesis of Compound **3a**. Cyclohexanone 0.490 g (5 mmol), benzaldehyde 1.061 g (10 mmol) and $InCl_3 \cdot 4H_2O$ 0.034 g (0.1 mmol) were placed in a glass tube and sealed. The sealed tube was placed in an oil bath and heated at 110°C for 6 h. After cooling to room temperature, the reaction mixture was ground with ethanol (20 mL), and filtered. The rude product was washed with water, saturated brine, and ethanol in turn. After drying in vacuum and recrystallization from ethanol, the crystalline product was afforded **3a** in 95% yield, M.p. 116–117°C (Lit.[9], 117°C), IR (KBr) 1663 (w), 1605 (m), 1445 (m), 1275 (m), 1146 (m), 772 (m), 696 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, TMS) δ ppm: 7.81 (s, 2H, =C-H), 7.50–7.30 (m, 10H, Ar-H), 2.94 (t, 4H, $J = 6$ Hz, 3, 5-CH_2), 1.86–1.74 (m, 2H, 4-CH_2).

Compound **3b.** M.p. 147–148°C (Lit.[11], 147–148°C). IR (KBr) 1667(w), 1576(s), 1489(s), 1404(m), 1264(s), 1159(s), 1092(s), 1009(m), 835(s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.73 (s, 2H, =CH), 7.39–7.36 (m, 8H, Ar-H), 2.93–2.86 (m, 4H, 3,5-CH_2), 1.84–1.81 (m, 2H, 4-CH_2).

Compound **3c.** M.p. 159°C (Lit.[10], 158.5°C). IR (KBr): 1669(w), 1588(m), 1512(s), 1343(s), 1265(m), 1142(w), 1107(w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.28 (d, $J = 8$ Hz, 4H, Ar-H), 7.81 (s, 2H, =CH), 7.60 (d, $J = 8$ Hz, 4H, Ar-H), 2.94 (t, $J = 8$ Hz, 4H, 3,5-CH_2) 1.89–1.86 (m, 2H, 4-CH_2).

Compound **3d.** M.p. 203–204°C (Lit.[9], 203–204°C). IR (KBr) 1657(w), 1593(m), 1555(m), 1509(s), 1451(w), 1418(w), 1248(s), 1161(m), 1024(s), 835(s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.76 (s, 2H, =CH), 7.46 (d, $J = 8.6$ Hz, 4H, Ar-H), 6.93 (d, $J = 8.6$ Hz, 4H, Ar-H), 3.84 (s, 6H, CH_3), 2.92 (t, $J = 5.4$ Hz, 4H, 3,5-CH_2), 1.86–1.74 (m, 2H, 4-CH_2).

Compound **3e.** M.p. 170°C (Lit.[10], 170°C). IR (KBr) 1661(m), 1601(s), 1564(m), 1508(m), 1410(m), 1267(s), 1140(m), 959(m), 660(w), 528(m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (s, 2H, =CH), 7.38 (d, $J = 8.2$ Hz, 4H, Ar-H), 7.21 (d, $J = 8.2$ Hz, 4H, Ar-H), 2.91 (t, $J = 7$ Hz, 4H, 3,5-CH_2), 2.39 (s, 6H, CH_3), 1.84–1.72 (m, 2H, 4-CH_2).

Compound **3f.** M.p. 189°C (Lit.[9], 188–189°C). IR (KBr) 1707(s), 1601(m), 1568(m), 1447(m), 1250(m), 1179(m), 932(m), 764(m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60 (s, 2H, =CH), 7.45–7.35 (m, 10H, Ar-H), 3.13 (s, 4H, 3,4-CH_2).

Compound **3g.** M.p. 231°C (Lit.[9], 230–231°C). IR (KBr) 1686(cm), 1605(m), 1522(s), 1343(s), 1252(w), 1184(m), 855(m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, $J = 8$ Hz, 4H, Ar-H), 7.75 (d, $J = 8$ Hz, 4H, Ar-H), 7.65 (s, 2H, =CH), 3.20 (s, 4H, 3,4-CH_2).

Compound **3h.** M.p. 211–212°C (Lit.[10], 212°C). IR (KBr) 1696(m), 1597(s), 1510(s), 1254(s), 1173(s), 1030(m), 835(m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.59–7.55 (m, 6H, Ar-H and =CH), 6.96 (d, $J = 8.8$ Hz, 4H, Ar-H), 3.86 (s, 6H, OCH_3), 3.08 (s, 4H, 3,4-CH_2).

Compound **3i.** M.p. 56–58°C (Lit.[10], 55–57°C). IR (KBr) 1684(w), 1657(s), 1594(s), 1512(s), 1262(s), 1171(m), 1017(m), 826(m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05–8.00 (m, 2H, Ar-H), 7.82 (d, $J = 15.8$ Hz, 1H, =CH), 7.67–7.40 (m, 9H, Ar-H and =CH).

Compound **3j.** M.p. 75–77°C (Lit.[10], 75–76°C). IR (KBr) 1659(s), 1599(s), 1512(s), 1445(w), 1339(m), 1264(s), 1211(m), 1169(m), 983(s), 779(s), 689(m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03–7.99 (m, 2H, Ar-H), 7.80 (d, $J = 15.4$ Hz, 1H, =C-H), 7.64–7.50 (m, 5H, Ar-H), 7.42 (d, $J = 15.4$ Hz, 1H, =CH), 6.94 (d, $J = 8.6$ Hz, 2H, Ar-H), 3.86 (s, 3H, OCH_3).

Compound **3k.** Oil (Lit.[10], b.p.164–165°C/10 torr). IR (CCl_4) 1713(s), 1644(w), 1464(s), 1416(m), 1381(m), 1254(m), 1152(s), 966(m), 777(w) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.30 (s, 1H), 6.34 (t, $J = 8.1$ Hz, 1H, =CH), 0.91 (t, $J = 7.2$ Hz, 3H, CH_3), 0.86 (t, $J = 7.2$ Hz, 3H, CH_3).

Compound **3l.** M.p. 115–116°C (Lit.[5], 114–116°C). IR (KBr) 1670(w), 1651(s), 1626(m), 1593(s), 1495(m), 1447(m), 1343(m), 1194(s), 982(m), 762(m), 556(w) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, $J = 16$ Hz, 2H, CH), 7.25–7.61 (m, 10H, Ar-H), 7.08 (d, $J = 16$ Hz, 2H, =CH).

Compound **3m**. Oil (Lit.[10], b.p.141–144°C/13 torr). IR (CCl_4) 1713(s), 1450(m), 1428(m), 1339(w), 1312(m), 1221(m), 1121(m), 1064(w), 909(w), 750(w) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.60 (t, $J = 7$ Hz, 1H, =CH), 4.30 (m, 1H), 2.31–2.37 (m, 2H, CH_2), 1.74–2.02 (m, 12H, CH_2), 1.63–1.73 (m, 2H, CH).

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