## Regio- and Diastereoselective Reduction of Nonenolizable $\alpha$ -Diketones to Acyloins Mediated by Indium Metal

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ABSTRACT



 $\alpha$ -Diketones are efficiently reduced with indium metal in methanol–water in the presence of NH<sub>4</sub>Cl, LiCl, or NaCl to give regio- and diastereoselectively the corresponding acyloins in good to excellent yield. The cleavage of the acyloins under Pb(OAc)<sub>4</sub>/MeOH–PhH condition provides a convenient and regioselective access to highly functionalized cyclopentane carboxaldehydes, potential building blocks in organic syntheses.

It is well-known that the acyloin ( $\alpha$ -hydroxyketone) functional group plays an important role in organic synthesis and is widespread in compounds of natural origin as well as in advanced intermediates en route to several target molecules.<sup>1</sup> Conventionally,  $\alpha$ -hydroxyketones are prepared by acyloin condensation reaction,<sup>2</sup> oxidation of enolates,<sup>3</sup> and reduction of  $\alpha$ -diketones.<sup>4</sup> However, the problems of over-reduction to a diol<sup>5</sup> or to an  $\alpha$ -methylene ketone<sup>6</sup> that are associated with reduction of  $\alpha$ -diketones make this procedure less attractive. Thallium(III)-promoted  $\alpha$ -oxidation of ketones to  $\alpha$ -acetoxy ketones is the most recent entry<sup>7</sup> to the growing

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list. Indium-mediated reactions have gained considerable importance in the recent past due to their mild nature, functional group tolerance, high stereoselectivity, ease of handling, and versatility of the reagent for a number of useful transformations that could be carried out even in water as solvent, without a need to rigorously exclude air.<sup>8</sup> However, there are limited number of reports in the literature on indium-mediated reductions.<sup>9</sup> In continuation of our work on indium-mediated reactions,<sup>10</sup> we report herein a mild, efficient, and stereoselective route to acyloins mediated by indium metal in MeOH and water in the presence of NH<sub>4</sub>-Cl, LiCl, or NaCl.

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The requisite  $\alpha$ -diketones **1a**-**26a** were prepared efficiently in excellent yields from the readily available Diels-Alder adducts<sup>11</sup> following a methodology developed recently

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in our laboratory.12 We first examined monosubstituted derivatives (Table 1).<sup>13</sup> The substrates 1a-12a were sub-

α-Diketones to Acyloins <sup>a</sup>										
$\begin{array}{c} MeO  OMe  MeO  MeO $										
entry	substrate	R	products	time (h)	yield (%) <sup>b</sup>	ratio <b>b</b> :c				
1	1a	Ph	1b,c	12	97	100:0				
2				13	95 <sup>c</sup>	100:0				
3				12	$95^d$	100:0				
4	2a	CH <sub>2</sub> OMe	2b,c	9	99	80:20				
5	3a	CH <sub>2</sub> OAc	3b,c	4	84	93:7				
6				15	96 <sup>e</sup>	64:36				
7	<b>4a</b>	OAc	<b>4b</b> ,c	12	68	100:0				
8				16	90 <sup>e,f</sup>	70:30				
9	5a	OEt	5 <b>b</b> ,c	12	100	71:29				
10	6a	CO <sub>2</sub> Me	6b,c	6	76 <sup>e</sup>	65:35				
11	7a	SiMe <sub>3</sub>	7b,c	7	96	81:19				
12	8a	Ph	<b>8b</b> ,c	4	52	100:0				
13				16	91 <sup>e</sup>	100:0				
14	9a	CH <sub>2</sub> OAc	<b>9b,c</b>	12	34	85:15				
15				5	<b>68</b> <sup>e</sup>	85:15				
16	10a	OAc	10b,c	6	40	100:0				
17				6	85 <sup>e,f</sup>	80:20				
18	11a	OEt	11b,c	9	83	81:19				
19	12a	CO <sub>2</sub> Me	12b,c	10	68 <sup>e</sup>	68:32				

Table 1. Indium-Mediated Reduction of Monosubstituted

<sup>*a*</sup> All reactions were run using 2 equiv of indium metal, and NH<sub>4</sub>Cl was used, unless otherwise specified. <sup>*b*</sup> Isolated yields of analytically pure **b**+**c**. <sup>c</sup> MeOH:10% HCl (4:1) without MCl. <sup>d</sup> NaCl was used. <sup>e</sup> THF:H<sub>2</sub>O (4:1). f LiCl was used.

jected to indium-mediated reductions in MeOH:H<sub>2</sub>O (4:1) at reflux temperature in the presence of NH<sub>4</sub>Cl, LiCl, or NaCl.<sup>14</sup> Both chloro and bromo derivatives underwent smooth transformation to the acyloins in a regio- and stereoselective manner to furnish 1b-12b as the major isomer and 2c-7c, 9c-12c as the minor isomer, probably via the protonation of the common acyloinate intermediate (Table 1). The substrates 1a and 8a furnished essentially a single regioisomer, 1b and 8b, respectively. The yields were

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generally high except in case of substrates 4a, 9a, and 10a (entries 7, 14, and 16). However, the yields in these cases could be considerably improved (entries 8, 15, and 17), albeit at the expense of diminished regioselectivity, by changing the solvent system to THF $-H_2O$  (4:1). This solvent system also gave satisfactory results in the case of ester derivatives 6a, 12a, 13a, and 16a, which reacted sluggishly in aqueous methanolic medium. The two solvent systems appear to play an important role with respect to the yield and regioselectivity of the products. In MeOH-H<sub>2</sub>O, the regioselectivity is high compared to aqueous THF, but for sensitive substrates the latter gives better results in terms of yield.

The derivatives 13a and 14a follow the same trend as the monosubstituted cases (Scheme 1), demonstrating that an



additional exo substituent placed either on the vicinal carbon or on the same carbon that bears the *endo* substituent has no influence on the regio- and diastereoselectivity (compare entries 1 and 10, Table 1).

The structural assignments in case of the products derived from the monosubstituted derivatives 1a-14a were made from their <sup>1</sup>H and <sup>13</sup>C NMR spectra. It is known that in bicyclo [2.2.1] systems the presence of an endo oxygen substituent at C<sub>2</sub> has a remarkable deshielding effect on the endo-H<sub>6</sub>. The exo-H<sub>6</sub> also experiences a shielding effect. The comparison of <sup>1</sup>H NMR (400 MHz) values of exo- and endo- $H_6$  of acyloins with those of the parent  $\alpha$ -diketone unambiguously confirms the stereochemical assignments.<sup>15</sup> In compounds 1b-14b the *endo*-H<sub>6</sub> clearly showed a consistent deshielding effect ranging from 0.2 to 0.5 ppm while the  $exo-H_6$  is shielded by 0.2 to 0.4 ppm. Further proof came from the W-coupling between the carbinol exo-H2 and the exo-H<sub>6</sub> (0.7–2.4 Hz). In <sup>13</sup>C NMR spectrum, C<sub>6</sub> is consistently shielded by 3-4 ppm due to endo-OH at C<sub>2</sub>.

In case of disubstituted derivatives 17a-26a, indiummediated reduction proceeds stereoselectively to furnish the acyloins 17b-26b (Table 2).<sup>13</sup> The diester derivatives 15a (X = H) and 16a gave the corresponding lactones 15c and 16c. The products 25d and 26d formed via over-reduction of 25a and 26a were characterized on the basis of the coupling shown by the bridgehead proton with the exo-H<sub>5</sub>

<sup>(12) (</sup>a) Khan, F. A.; Prabhudas, B.; Dash, J.; Sahu, N. J. Am. Chem. Soc. 2000, 122, 9558. The full details of the preparation of some new diketones reported in the present paper will be published in a full account in the near future.

<sup>(13)</sup> All new compounds gave satisfactory analytical and spectral data. (14) General procedure for the indium-mediated reduction of  $\alpha$ -diketones: A mixture of  $\alpha$ -diketone (0.3 mmol), indium metal (0.6 mmol, cut into small pieces), and NH<sub>4</sub>Cl (0.9 mmol) in MeOH (4 mL) and water (1 mL) was refluxed for the specified time (Tables 1 and 2 and Scheme 1). After completion of the reaction, as monitored by TLC, the reaction mixture was quenched with 3 mL of 5% HCl and extracted with ethyl acetate. The combined organic layer was washed once with brine and dried over anhydrous Na2SO4. Concentration followed by silica gel column chromatography gave the acyloins in the specified yields.

<sup>(15)</sup> A deatailed comparison in tabular form is presented in the Supporting Information.

**Table 2.** Indium-Mediated Reduction of Disubstituted  $\alpha$ -Diketones to Acyloins<sup>*a*</sup>

	McO O O X R X=H 15a X=Cl 16a-22 X=Br 23a-26	Me K $R$ $MeOH-H_2O (4)$ reflux $M=NH_4$ , Li or N a a	$\begin{array}{c} M \\ O \\ \vdots \\ 1) \\ Na \\ X=0 \\ X=E \end{array}$	eO C X R Cl 17b-22 Sr 23b-26	DMe X R R b
entry	substrate	R	product	time (h)	yield (%) <sup>b</sup>
1	150	<u>CO-Ma</u>	150	15	71
1	15a 10-		10.	15	/1
z	16a	CO <sub>2</sub> Me	160	23	83°
3	17a	CH <sub>2</sub> OAc	17b	14	<b>88</b> <sup>a</sup>
4	18a	-CH <sub>2</sub> OCH <sub>2</sub> OCH <sub>2</sub> -	18b	6	94
5	19a	-(CH <sub>2</sub> ) <sub>3</sub> -	19b	8	100
6	20a	-(CH <sub>2</sub> ) <sub>4</sub> -	20b	7	100
7				5	100 <sup>e</sup>
8	21a	-(CH <sub>2</sub> ) <sub>6</sub> -	21b	7	100
9	22a	-CH2OCH2-	22b	11	95
10	23a	CH <sub>2</sub> OAc	23b	6	67 <sup>c,d</sup>
11	24a	-CH <sub>2</sub> OCH <sub>2</sub> OCH <sub>2</sub> -	24b	7	72 <sup>c,d</sup>
12	25a	-(CH <sub>2</sub> ) <sub>4</sub> -	25b.d	6	72.13 <sup>c</sup>
13	26a	-CH2OCH2-	26b,d	8	$22, 44^d$

 $^a$  All reactions were run using 2 equiv of indium metal ,and NH<sub>4</sub>Cl was used, unless otherwise specified.  $^b$  Isolated yields of analytically pure sample.  $^c$  THF:H<sub>2</sub>O (4:1).  $^d$  LiCl was used.  $^e$  NaCl was used.



and W-coupling between the carbinol *exo*- $H_2$  and the *exo*- $H_6$ . The characteristic signals for a bromine-bearing bridgehead and carbinol carbon at 67.2, 83.2 ppm for **25d** and at 63.0 and 83.0 for **26d** in <sup>13</sup>C NMR spectrum unambiguously confirmed the structural assignment.

Further, the method was successfully employed for the smooth reduction of benzil to benzoin **27** in high yield. The reduction of camphorquinone also proceeded efficiently in quantitative yield in MeOH $-H_2O$ , giving rise to a 1:1 mixture of regioisomers **28** and **29** (Figure 1). The structural assignments in this case were based on the literature report.<sup>16</sup>





After successfully developing the methodology for the regioselective reduction of diketones, it occurred to us that the cleavage of acyloin, particularly for monosubstituted norbornyl derivatives, could be highly fruitful in achieving stereoselective transformation and may lead to derivatives that are not easily accessible otherwise. For example, the attempted selective reduction of **1f** (obtained from **1a**)<sup>12</sup> using 1 equiv of DIBAL-H at -78 °C furnished a mixture, thus disqualifying this as a useful route to aldehyde **1e**. On the other hand, treatment of acyloin **1b**, obtained via indium reduction of **1a**, furnished the aldehyde **1e** in good yield upon treatment with Pb(OAc)<sub>4</sub> in MeOH–PhH (3:1),<sup>17</sup> thus constituting an efficient and stereoselective route to highly functionalized cyclopentane carboxaldehydes (Scheme 2).



The procedure was efficiently extended to other derivatives **4b**, **5b**, **7b**, and **11b** to obtain the corresponding cyclopentane carboxaldehydes in good yield.

In summary, we have described a novel, efficient, and regio- as well as diastereoselective conversion of nonenolizable bicyclic  $\alpha$ -diketones into synthetically useful acyloins mediated by indium metal, tolerable to a variety of sensitive substituents such as acetate, ester, and bridgehead halogens. Further, the methodology is extended to the synthesis of highly functionalized cyclopentane carboxalde-hydes, potential building blocks in organic syntheses, via

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<sup>(17)</sup> General procedure for the cleavage of acyloins: To a stirred solution of the acyloins (0.2 mmol) in MeOH (3 mL) and benzene (1 mL) was added Pb(OAc)<sub>4</sub> (0.5 mmol) in portions over a period of 15 min at room temperature. After stirring for the required time (monitored by TLC, Scheme 2), 3 mL of water was added and the reaction mixture extracted with ethyl acetate. The combined organic layer was washed with water, once with a dilute NaHCO<sub>3</sub> solution, and once with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration followed by silica gel chromatography of the crude yielded the pure cyclopentane carboxal dehydes.

cleavage of the acyloins under  $Pb(OAc)_4/MeOH-PhH$  conditions.

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**Supporting Information Available:** Spectral and analytical data for all acyloins and cyclopentane carboxaldehydes. This material is available free of charge via the Internet at http://pubs.acs.org.

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