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# A facile synthesis of 7-amino-3-desacetoxycephalosporanic acid derivatives by indium-mediated reduction of 3-iodomethylcephems in aqueous media

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## Abstract

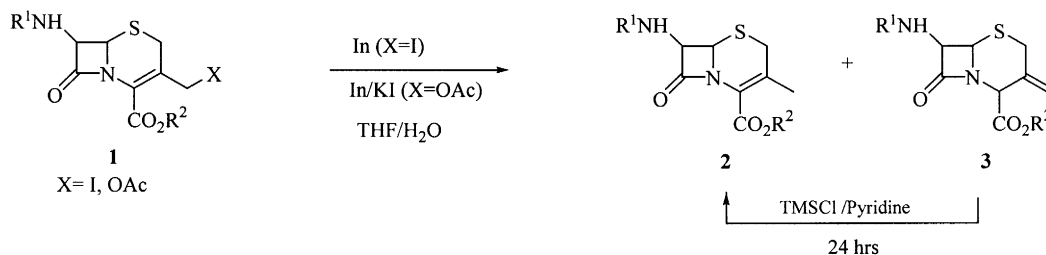
An efficient reductive conversion of 3-iodomethylcephalosporin and 3-acetoxymethylcephalosporin derivatives mediated by indium into the corresponding 3-methylcephems and 3-methylenecephems in moderate to good yields has been developed in an aqueous system. 3-Methylenecephems are converted into the corresponding 3-methylcephems under previously reported basic conditions quantitatively. © 2000 Elsevier Science Ltd. All rights reserved.

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3-Methylcephem (**2**) is a key intermediate for the preparation of novel oral cephem antibiotics such as cephalixin,<sup>1</sup> cephradine,<sup>2</sup> cephadroxil,<sup>3</sup> cefetamet pivoxil,<sup>4</sup> etc. Several methods have been known for the synthesis of these compounds: isomerization of 3-methylenecephems under basic conditions,<sup>5</sup> hydrogenolysis of 7-ACA derivatives,<sup>6</sup> electrochemical reduction of cephalosporanic acids<sup>7</sup> and ring expansion of penicillin sulfoxides.<sup>8–10</sup> Herein we wish to report a new and convenient synthesis of 7-amino-3-desacetoxycephem derivatives by the reduction of 3-iodomethylcephem with indium in aqueous media (Scheme 1). Although many indium mediated organic transformation reactions have been reported,<sup>11–14</sup> there have been relatively few reports<sup>15</sup> on the use of indium metal in dehalogenation reactions.

Thus treatment of iodomethylcephems **1** (entries a–c, Table 1), prepared from commercially available 3-chloromethylcephems **1** (X=Cl) by the known method,<sup>16,17</sup> with 2 equimolar amounts of indium powder in a 1:1 mixture of H<sub>2</sub>O and THF at room temperature for 2 h gave a 1:1.2 mixture of **2** and **3** in 60–74% yields. With 3-acetoxymethylcephems (entries d–h) synthesized from 7-ACA,<sup>17</sup> the compounds were reacted with 200 M% of KI<sup>18</sup> then dehalogenated with 2 equimolar amounts of indium in situ in a 1:1 mixture of H<sub>2</sub>O and THF at 40–60°C to produce a mixture of **2** and **3** in 71–79% yields.

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Scheme 1.

The crude mixture products were treated without purification with 120 M% of trimethylsilyl chloride in the presence of pyridine for 24 h at room temperature<sup>19</sup> to yield the compound **2** as a sole product as shown in Table 1. This reaction is particularly attractive since 7-ACA (**1h**) can be transformed into 7-ADCA (**2h**) without protection of the amine and carboxylic acid functional groups of 7-ACA. The compound **3h** is transformed into **2h** quantitatively using *N*-trimethylsilylacetamide and triethylamine.<sup>20</sup> Although a variety of reaction conditions using other metals such as zinc or tin were explored, no dehalogenation of cepheems was observed except zinc/ammonium chloride conditions<sup>21</sup> which gave 3-exomethylenecephems **3a** exclusively in poor yield (15%). A typical procedure is as follows. To a solution of 7-amino-3-acetoxymethyl carboxylic acid (100 mg, 0.367 mmol) in 3 ml of THF:H<sub>2</sub>O (1:1), 200 M% of indium powder (–100 mesh, 0.085 g) and KI (0.060 g, 200 M%) were added successively. The reaction mixture was heated at 60°C for 4 h, cooled to room temperature, and then 1 ml of 1N HCl and 2 ml of CH<sub>3</sub>CN were added and filtered off the indium residue. The filtrate was neutralized by dilute aqueous NaHCO<sub>3</sub> solution and the precipitate was dried under vacuum. The crude mixture was dissolved in 5 ml of CH<sub>3</sub>CN and reacted with *N*-trimethylsilylacetamide (144 mg, 1.10 mmol) for 0.5 h. Triethylamine (0.3 ml, 0.004 mmol) was added to the clear solution and the reaction mixture was stirred for 3 h followed by addition of 3 ml of MeOH. The solution was acidified with 0.1N HCl to pH 3.6 to precipitate 62 mg (78%) of **2h**.

Table 1

Entry	X	R <sup>1</sup>	R <sup>2</sup>	Temp. (°C)	Time (hrs)	Yield of (2 + 3) (%)	Ratio of (2/3)	Total Yield(2) (%)
a	I <sup>†</sup>	PhCH <sub>2</sub> CO-	PMB	r.t.	2	74	1 : 1.2	73
b	I	PhCO-	PMB	r.t.	2	63	1 : 1.2	62
c	I	PhOCH <sub>2</sub> CO-	PMB	r.t.	2	60	1 : 1.2	58
d	OAc <sup>‡</sup>	PhCH <sub>2</sub> CO-	H	50	3	71	1 : 1.3	70
e	OAc	PhCH <sub>2</sub> CO-	PMB	45	3	75	1 : 1.3	73
f	OAc	PhCH <sub>2</sub> CO-	DPM	45	3	79	1.3 : 1	76
g	OAc	PhCO-	H	50	3	70	1 : 1.3	65
h	OAc	H	H	60	4	79	1 : 1.5	<sup>§</sup> 78

<sup>†</sup> 2.0 equimolar amounts of In were used. <sup>‡</sup> 2.0 equimolar amounts of In and KI were used.

<sup>§</sup> TMSA/TEA conditions were used. PMB = *p*-methoxybenzyl, DPM = diphenylmethyl

In conclusion we could demonstrate that indium can dehalogenate 3-iodomethylcephems in aqueous media and extend the scope of indium utility in organic synthesis. Further studies on the use of indium in aqueous media are in progress.

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