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Reductive Cyclodimerization of Arylidenecyanoacetates Promoted by $Sm/InCl_3 \cdot 4H_2O$ System in Aqueous Media

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Abstract: Promoted by active indium produced *in situ* by $Sm/InCl_3 \cdot 4H_2O$ system, arylidenecyano- acetates undergo reductive cyclodimerization to afford cyclopentamine derivatives with high stereoselectivity under mild conditions in aqueous media.

Keywords: Indium, active metal, cyclopentamine, reaction in aqueous media.

Metal-mediated reactions in aqueous media have received considerable attention in the last decade[1]. Such aqueous reactions offer a number of advantages over conventional organometallic reactions in organic solvent in that they are practically convenient, environmentally benign and do not require strict anhydrous conditions[2]. In recent years, besides zinc and tin, indium has been found to be the metal of choice for promoting organic reactions in aqueous media[3]. Indium is considered to be more effective than zinc and tin, the reactions mediated by indium require no activation and the side products are few. Although indium has been used extensively in the generation of synthetically useful allylindium species[4], its use in other domains has not been explored[5]. Thus it is necessary to extend the applications of indium in organic synthesis in aqueous media.

Meanwhile, since the general approach for the preparation of highly reactive metal powders was reported in 1972[6], active metals have attracted considerable attention in organic synthesis[7]. Due to the high reactivity of active metals, reactions are typically carried out more efficiently, under milder conditions, and with a wider array of substrates than with other methods. Herein we wish to report the active metallic indium produced *in situ via* $Sm/InCl_3 \cdot 4H_2O$ system in THF-H_2O (8/1) mixture in open air, and its application in reductive cyclodimerization of arylidenecyanoacetates **1** to afford cyclopentamine derivatives **2** with high stereoselectivity (*trans*, *trans*-form) under mild conditions (**Scheme 1**). The results are shown in **Table 1**.

When indium(III) chloride suspended in THF-H_2O (8/1) mixture was treated with metallic samarium at room temperature, drastic reaction took place, and a kind of light black species appeared in 3 minutes, which indicated that active metallic indium has been prepared. Subsequent treatment of arylidenecyanoacetates **1** with the active

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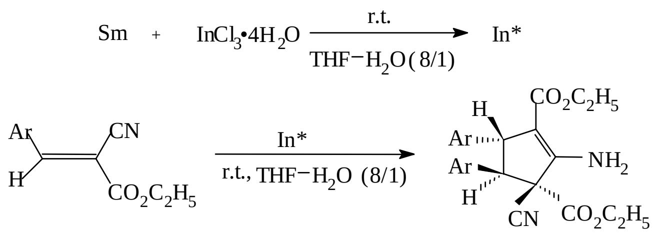
indium formed *in situ* gave cyclopentamine derivatives **2**[8] in good yields. Through careful separation of the reaction mixture, only one isomer, the *trans*, *trans* isomer, was obtained, indicating that this cyclodimerization process is highly stereoselective. It has also been found that the chloro, bromo and alkoxyl groups of the substrates were tolerated under the reaction conditions. It should be noted that no reaction took place with either metallic samarium or indium trichloride or metallic indium alone even after 20 hours.(**Table 1**, Entry **2a**).

Scheme 1



1 **2a~i**

2a: Ar=C_6H_5; **2b**: Ar=4-$CH_3C_6H_4$; **2c**: Ar=4-$CH_3OC_6H_4$; **2d**: Ar=4-BrC_6H_4; **2e**: Ar=2-BrC_6H_4; **2f**: Ar=3-BrC_6H_4; **2g**: Ar=4-ClC_6H_4; **2h**: Ar=3,4-$OCH_2OC_6H_3$; **2i**: Ar=furyl

Table 1 Reductive coupling cyclization of arylidenecyanoacetates promoted by Sm/$InCl_3$•$4H_2O$ system in aqueous media

Compound	Ar	Reaction time (h)	Mp (°C) (lit.[9d])	Yield (%)[a]
2a	C_6H_5	1.2 (20[b], 20[c])	172-174 (172-174)	86 (0[b], 0[c])
2b	4-$CH_3C_6H_4$	1.2	189-192 (189-191)	84
2c	4-$CH_3OC_6H_4$	1.2	159-162 (160-162)	83
2d	4-BrC_6H_4	1.2	190-192 (192-194)	87
2e	2-BrC_6H_4	1.5	191-192 (192-194)	80
2f	3-BrC_6H_4	1.5	150-152 (150-152)	79
2g	4-ClC_6H_4	1.2	177-180 (178-180)	85
2h	3,4-$OCH_2OC_6H_3$	1.5	185-187 (186-187)	80
2i	2-furyl	2	131-134 (131-134)	71

[a]Isolated yields. [b]In the presence of Sm powder or $InCl_3$•$4H_2O$ alone. [c]Metallic indium was used under the same reaction conditions.

Reductive dimerization of carbonyl derivatives by means of active metals is one of the most valuable methods for establishing carbon-carbon bonds[9]. Recently, some reports on the reductive cyclodimerization of α, β-unsaturated carbonyl derivatives or electron-deficient olefins have already been reported, providing a novel access to functionalized five-membered ring products[10]. Compared with reagents such as SmI_2[10c], Sm/THF-NH_4Cl (aq.)[10d], Zn/THF-NH_4Cl (aq.)[11] *etc.* systems, which have been successfully used in promoting reductive cyclodimerization of arylidenecyanoacetates, the present procedure provided a new approach to synthesize cyclopentamine derivatives with high yields, simple and environmentally benign reaction conditions and high chemo- and stereoselectivity. Further studies to develop the Sm/$InCl_3$ • $4H_2O$ system in organic synthesis are now in progress in our laboratory.

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