SHORT PAPER

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Reductive cyclodimerisation of arylmethylidenemalononitriles promoted by SM/$InCl_3$·$4H_2O$ system in aqueous media: highly stereoselective synthesis of cyclopentamine derivatives†

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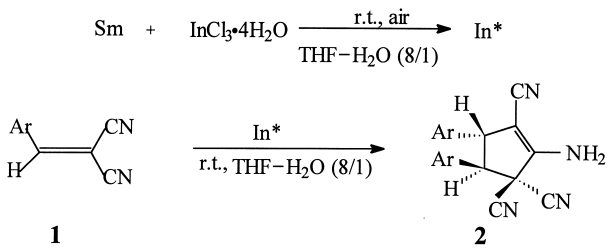
In the presence of active indium produced *in situ* by the Sm/$InCl_3$·$4H_2O$ system, arylmethylidenemalononitriles undergo reductive cyclodimerisation to afford cyclopentamine derivatives with high stereoselectivity under mild conditions in aqueous media.

Keywords: reductive cyclodimerisation, arylmethylidenemalononitriles

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 an organic solvent.[2] They are technically convenient, environmentally friendly and do not require anhydrous organic solvents. Recently, indium has been found by Chan to be the metal of choice in place of zinc and tin.[3] Indium is considered to be more effective than zinc and tin since the reaction requires no activation and produces only few side products. Although indium has been used extensively in the generation of synthetically useful allylindium species,[4] its use in other domains has not been explored to any great extent.[5] Thus it would seem reasonable to develop other application of indium in organic synthesis.

Since a 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] Because of 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 current methods. Here we wish to report that active metal indium is easily produced *in situ via* SM/$InCl_3$·$4H_2O$ system in THF–H_2O mixture in open air. Promoted by this active species, arylmethylidenemalononitriles undergo reductive cyclodimerisation to afford cyclopentamine derivatives with high stereoselectivity giving the *trans* form under mild conditions in aqueous media (Scheme 1). The products and the reaction conditions are shown in Table 1.

When $InCl_3$·$4H_2O$ suspended in THF-H_2O (8/1) mixture was treated with samarium in open air, a rapid reaction took place, and a light black species appeared in 3 minutes which indicated



Scheme 1

Table 1 Reductive coupling cyclization of arylmethylidenemalononitriles (**1**) promoted by Sm/$InCl_3$·$4H_2O$ system in aqueous media

Entry	Ar	Reaction time/h	Yield/%[a]
1	C_6H_5	0.5 (20[b], 20°[c])	89 (0[b], 0[c])
2	4-$CH_3C_6H_4$	0.5	87
3	4-$CH_3OC_6H_4$	0.5	83
4	4-BrC_6H_4	0.5	90
5	3-BrC_6H_4	1	86
6	4-ClC_6H_4	0.5	88
7	3,4-$OCH_2OC_6H_3$	1	78
8	2-furyl	2	74

[a]Isolated yield. [b]In the presence of SM powder or $InCl_3$ alone. [c]Metal indium was used in the same reaction conditions.

that active metal indium was readily prepared. Treatement of arylmethylidenemalononitriles with this species produced cyclopentamine derivatives **2**. Through careful separation of the reaction mixture, only one isomer, the 4,5-*trans* isomer, was obtained, indicating that this cyclodimerisation process is highly stereo-selective. We found that the chloro, bromo and alkoxyl groups in the substrates were tolerated under the reaction conditions. In addition, it should be noted that no reaction took place with either metal samarium or indium trichloride alone (Table 1, Entry **1**). When metal indium was used under the same conditions even over 20 hours reaction time, neither cyclodemerisation nor carbon–carbon bond reductive products[5] were obtained (Entry **1**).

Several reagents have been used for reductive cyclodimerisation of α,β-unsaturated nitriles, such as SmI_2,[8] Zn/$TiCl_4$ system,[9] $CpVCl_2$/Me_3SiCl/Zn system,[10] Sm/THF-NH_4Cl(aq.) system.[11] However, these reagents have one or more limitations with regard to operational convenience (under N_2 atmosphere, without water).[8–10] not high yields[9] and not high stereoselectivity.[10,11] The present procedure provided a new route to cyclopentamine derivatives with advantages of high yields, simple, mild and environmentally friendly reaction conditions, and high chemo- and stereoselectivity. Futher studies to develop other uses of Sm/$InCl_3$·$4H_2O$) system are now in progress in our laboratory.

Experimental

Melting points were uncorrected. ^1H NMR spectra were recorded on a Bruker AC 300 instrument. All samples were measured in $CDCl_3$ using TMS as internal standard, IR spectra were determined on a Perkin-Elmer 683 spectrometer. The reactions were performed in open air.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

General procedure: In a 50 ml three-necked flask were placed $InCl_3{\cdot}4H_2O$ (0.22 g, 0.75 mmol), Sm (0.113 g, 0.75 mmol), THF (4 ml), then water (0.5 ml) was slowly added to the mixture. Vigorous reaction took place, and a light black species appeared in 3 minutes which indicated that active metal indium was readily prepared. The α,β-unsaturated nitriles (1 mmol) were then added to the flask. After stirring at room temperature for the time given in Table 1, the mixture was quenched with dil. HCl (0.1 mol/dm^3, 5 ml) and extracted with ether (3 ∞ 20 ml). The combined extract was washed with saturated brine (15 ml) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the resulting crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:4) as eluent.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-diphenylcyclopentene **2a**:[8] m.p. 127–129°C (Lit. 128–130°C); δ_H 3.78 (d, 1H, *J* 9.4 Hz, ArCH), 4.50 (d, 1H, *J* 9.4 Hz, ArCH), 5.32 (br s, 2H, NH_2), 7.12–7.68 (m, 10H, ArH); ν_{max}/cm^{-1}; 3385, 3230 (NH_2), 2212 (CN), 1668 (C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(4-methylphenyl)cyclopentene **2b**:[8] m.p. 190–192°C (Lit. 190–192°C); δ_H 2.24 (s, 3H, CH_3), 2.32 (s, 3H CH_3), 3.78 (d, 1H, *J* 9.6 Hz, ArCH), 4.54 (d, 1H, *J* 9.6 Hz, ArCH), 5.44 (br s, 2H, NH_2), 7.02–7.46 (m, 8H, ArH); ν_{max}/cm^{-1}: 3375, 3260 (NH_2) 2220 (CN), 1665 (C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(methoxyphenyl)cyclopentene **2c**:[8] m.p. 94–96°C (Lit. 95–97°C; δ_H 3.74 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.18 (d, 1H, *J* 9,6 Hz, ArCH), 4.49 (d, 1H, *J* 9.6 Hz, ArCH), 5.34 (br s, 2H, NH_2), 6.79–7.41 (m, 8H, ArH); ν_{max}/cm^{-1}: 3385, 3290 (NH_2), 2215 (CN), 1680 (C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(4-bromophenyl)cyclopentene **2d**:[8] m.p. 144–146°C (Lit. 145–147°C); δ_H 3.74 (d, 1H, J 9.6 Hz, ArCH), 4.50 (d, 1H, *J* 9.6 Hz, ArCH), 5.51 (br s, 2H NH_2), 7.02–7.61 (m, 8H, ArH); ν_{max}/cm^{-1}: 3380, 3220 (NH_2), 2215 (CN), 1680 (C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(3-bromophenyl)cyclopentene **2e**:[8] m.p. 116–118°C (Lit. 116–118°C); δ_H 3.64 (d, 1H, *J* 9.5 Hz, ArCH), 4.51 (d, 1H, *J* 9.4 Hz, ArCH), 5.46 (br s, 2H, NH_2), 7.10–7.68 (m, 8H, ArH); ν_{max}/cm^{-1}: 3378, 3320 (NH_2), 2210 (CN), 1670 C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(3-chlorophenyl)cyclopentene **2f**:[8] m.p. 1.75–177°C (Lit. 176–178°C); δ_H 3.75 (d, 1H, *J* 9.6 Hz, ArCH), 4.52 (d, 1H, *J* 9.6 Hz, ArCH), 5.48 (br s, 2H, NH_2), 7.01–7.60 (m, 8H, ArH); ν_{max}/cm^{-1}: 3380, 3270 (NH_2), 2215 (CN), 1670 (C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(3,4-methylenedioxyphenyl) cyclopentene **2g**:[8] m.p. 165–167°C (Lit. 166–168°C); δ_H 4.16 (d, 1H, *J* 7.8 Hz, ArCH), 4.44 (d, 1H, *J* 7.8 Hz, ArCH). 5.46 (br s, 2H, NH_2), 5.92 (s, 2H, OCH_2O), 5.97 (s, 2H, OCH_2O), 6.26–6.82 (m, 6H, ArH); ν_{max}/cm^{-1}: 3385, 3280 (NH_2), 2210 (CN), 1678 (C = C–NH_2) cm^{-1}.

(4R, 5R)-2-amino-1,3,3-tricyano-4,5-di(2-furyl)cyclopentene **2h**:[8] m.p. 124–126°C (Lit. 125–127°C); δ_H 4.20 (d, 1H, *J* 9.2 Hz, ArCH), 4.64 (d, 1H, *J* 9.2 Hz, ArCH), 5.64 (br s, 2H, NH_2), 6.34–7.59 (m, 6H, ArH); ν_{max}/cm^{-1}: 3390, 3285 (NH_2), 2218 (CN), 1670 (C = C–NH_2) cm^{-1}.

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