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An $InCl_3$ catalyzed facile one-pot synthesis of novel dispiro[cyclopent-3′-ene]bisoxindoles

Gnanamani Shanthi, Paramasivan T. Perumal *

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India

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ABSTRACT

An $InCl_3$ catalyzed efficient synthesis of novel dispiro[cyclopent-3′-ene]bisoxindoles is accomplished via a one-pot reductive cyclization of isatylidene malononitriles using the Hantzsch ester.

The indole template is generally recognized as an important structure in medicinal chemistry, and in particular, oxindoles that incorporate a quaternary stereogenic centre at C3 are attractive targets in organic synthesis because of their significant biological activities.[1] Among them, the spirooxindole framework represents an important structural motif present in a number of bioactive natural products such as coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine and alstonisine.[2] The unique structural array and the highly pronounced pharmacological activity displayed by this class of spirooxindoles have made them attractive synthetic targets. To the best of our knowledge, there are no reports on the synthesis of dispiro[cyclopent-3′-ene]bisoxindoles.

Chemical hydrogenation of double bond-containing compounds including imines, arylmethylidenemalononitriles and various other α,β-unsaturated systems often involves the use of metal catalysts[3] or stoichiometric amounts of metal hydrides.[4] Zhang et al. reported the intermolecular and intramolecular reductive coupling reactions of arylmethylidenemalononitriles induced by SmI_2[5] and also with Sm/TMSCl.[6] Vanadium catalyzed stereoselective cyclodimerization of arylidenemalononitrile in the presence of chlorosilane and zinc was also reported.[7] Itoh et al. examined the reaction of substituted dicyanoalkenes with aqueous titanium(III) chloride.[8] In these cases, there are drawbacks such as the use of expensive and even toxic metals, and relatively low chemoselectivity. To circumvent these problems one of the best alternatives is to apply organoreductants, which have aroused great interest in recent years.[9] As a typical example among these organoreductants, Hantzsch 1,4-dihydropyridine (HEH), which possesses excellent reducibility, has been thoroughly investigated.[10] In most cases, it was used as a model of the hydride-reduction cofactor NAD(P)H to mimic biological reductions of various unsaturated compounds. Tremendous efforts were devoted to the study of the mechanistic details of these systems,[11] and relatively little attention has been paid to the application of HEH as a reducing agent in organic synthesis. Garden et al.[12] reported that the Hantzsch ester quantitatively reduced isatylidene malononitriles to the corresponding 2-(2-oxo-2,3-dihydro-1*H*-3-indolyl)malonitriles. Hence, we investigated the reaction of the Hantzsch ester with two molecules of isatylidene malononitrile. To the best of our knowledge, this is the first time, the Hantzsch ester has been used for the reductive cyclization of isatylidene malononitriles to yield the trans isomers of dispiro[cyclopent-3'-ene]bisoxindoles. Herein, we describe our results on the $InCl_3$ catalyzed novel reductive cyclization of isatylidene malononitriles using the Hantzsch ester (Scheme 1).

In our initial endeavour, we investigated the reaction of Hantzsch ester **2** with two molecules of isatylidene malononitrile **1** in the presence of various Lewis acids. The catalytic effect of several Lewis acids was examined to determine the best catalyst, and the results are listed in Table 1.

It can be seen from Table 1 that all the Lewis acids promoted the reaction to a certain extent, however, $InCl_3$ (entry 5) demonstrated superior catalytic activity. In the absence of Lewis acid catalyst, the reaction was very slow and the product was obtained in trace (entry 1). This result prompted us to select $InCl_3$ as the catalyst for further study. Optimum results were obtained using 20 mol % of $InCl_3$.

Table 2 summarizes our results on the one-pot reaction of various isatylidene malononitriles with the Hantzsch ester[13]

* Corresponding author. Tel.: +91 44 24913289; fax: +91 44 24911589.
E-mail address: ptperumal@gmail.com (P. T. Perumal).

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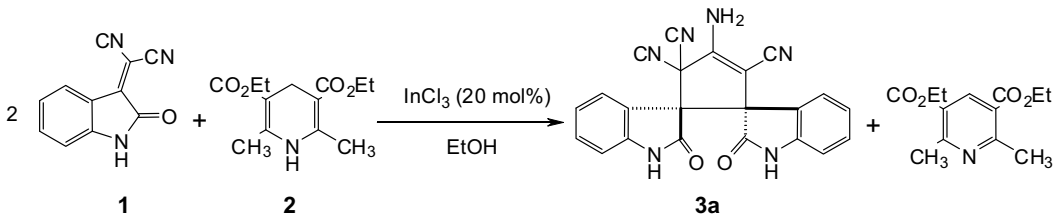


Scheme 1.

Table 1
Catalytic activity of various Lewis acids in the one-pot reductive cyclization of isatylidene malononitrile **1** with Hantzsch ester **2**

Entry	Catalyst	Yield (%)
1	None	Trace
2	$SnCl_2{\cdot}2H_2O$	42
3	$BiCl_3$	56
4	CAN	52
5	$InCl_3$	88
6	$In(OTf)_3$	74

Table 2
Synthesis of dispiro[cyclopent-3′-ene]bisoxindoles

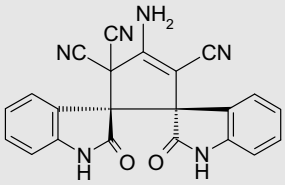
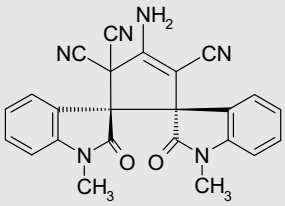
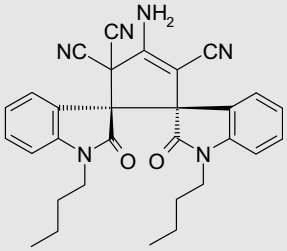
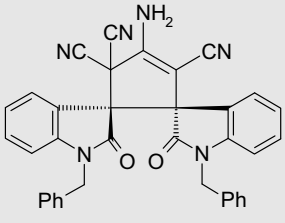
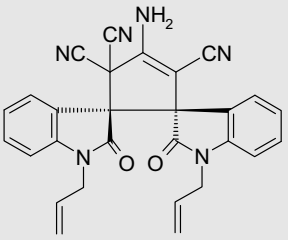
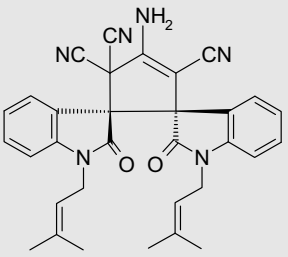
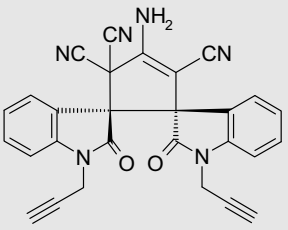
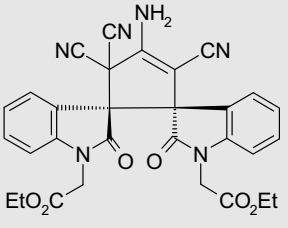
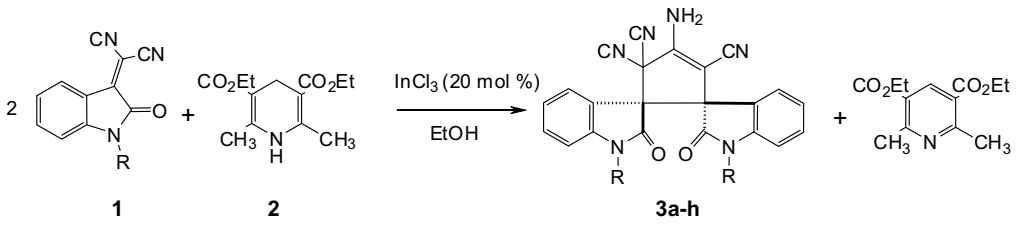
Entry	Product (**3**)	Time (min)	Yield[a] (%)
1	 **3a**	90	88
2	 **3b**	80	86
3	 **3c**	90	82
4	 **3d**	80	88

Table 2 (*continued*)

Entry	Product (**3**)	Time (min)	Yield[a] (%)
5	 **3e**	85	85
6	 **3f**	85	86
7	 **3g**	80	85
8	 **3h**	100	85

[a] Isolated yield.

(Scheme 2). All the reactions proceeded smoothly and afforded the trans isomers of corresponding substituted dispiro[cyclopent-3′-ene]bisoxindoles in good yields.[14] The reactions were stereoselective, as only one isomer was obtained and careful analysis of the reaction mixture indicated the absence of any other stereoisomer.



Scheme 2.

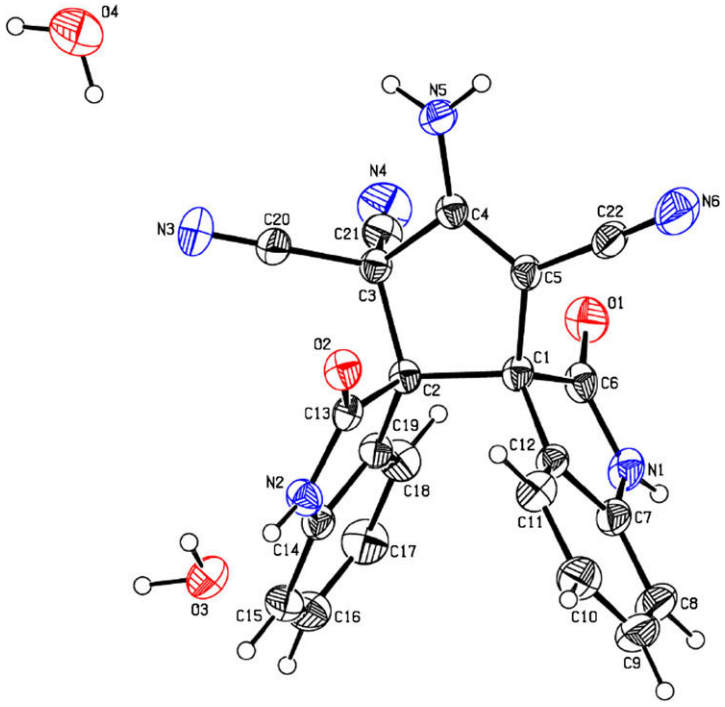
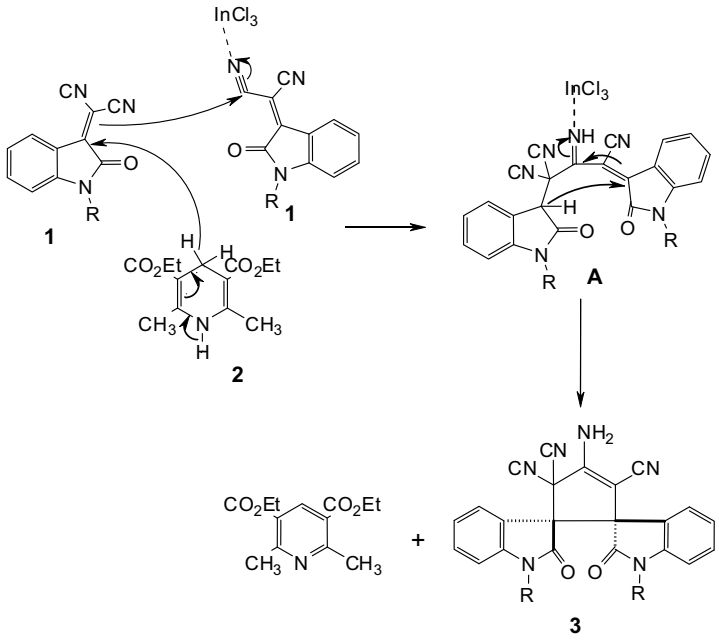


Figure 1. ORTEP diagram of compound **3a**.



Scheme 3.

The structures of compounds **3a–h** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **3a**[15] displayed the molecular ion (M^+) peak at *m/z* 392. The ^{1}H NMR spectrum of **3a** exhibited a broad singlet at δ 8.33 due to the NH_2 protons and signals at δ 10.73 and 11.18 (–NH groups) confirmed the incorporation of two oxindole rings in the structure. Resonances at δ 62.6 and 62.9 (two spiro carbons) and δ 173.1 and 176.8 (two carbonyl groups) were observed in the ^{13}C NMR spectrum. The IR spectrum showed absorptions at 3336 and 3188 (–NH_2), 2214 (–CN), 1725 (–C=O) and 1666 (–C=C–) cm^{-1}, respectively. The structure **3a** was further confirmed by a single crystal X-ray analysis, which clearly illustrated the trans stereochemistry (Fig. 1).[16]

Though the detailed mechanism of the above reductive cyclization has not been clarified yet, the formation of dispiro[cyclopent-3′-ene]bisoxindoles **3a–h** may be explained by the possible mechanism presented in Scheme 3.

The reaction may take place via hydride transfer from Hantzsch dihydropyridine ester **2** to the substrate **1** which then attacks another molecule of substrate to form intermediate **A**. Intermediate **A** then reacts intramolecularly to give product **3**.

In conclusion, we have demonstrated a novel, $InCl_3$ catalyzed, one-pot, reductive cyclization of isatylidene malononitriles using the Hantzsch ester for the synthesis of new dispiro[cyclopent-3′-ene]bisoxindoles in good yields. Biological evaluation of these derivatives is underway. Further studies to develop other new reactions using Hantzsch esters are now in progress.

Acknowledgement

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13. Several Hantzsch dihydropyridine derivatives were synthesized and applied in this reaction. Other 4,4-dihydro derivatives afforded the expected products, but the yields were slightly lower than with **2**. 4-Substituted (alkyl or aryl) Hantzsch dihydropyridines did not react under these conditions.
14. *General procedure for the synthesis of dispiro[cyclopent-3′-ene]bisoxindoles* **3a–h**: To a stirred mixture of isatylidene malononitrile (2 mmol) and Hantzsch dihydropyridine ester (1 mmol) in ethanol (10 mL), a catalytic amount of $InCl_3$ (20 mol %) was added and the reaction mixture was stirred at room temperature for about 1–2 h. After complete conversion, as indicated by TLC, the reaction mixture was poured into water and extracted with ethyl acetate (2 × 25 mL). The combined extract was dried over anhydrous Na_2SO_4 and concentrated in vacuum. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 4:6) to afford the pure product.
15. *4′-Amino-2,2″-dioxo-2,2″,3,3″-tetrahydro-1H-indole-3-spiro-1′-cyclopent-3′-ene-2′-spiro-3″-1H-indole-3′,5′,5′-tricarbonitrile* **3a** (Table 1, entry 1): White solid. mp: 232–233 °C. ν_{max} (KBr): 3336, 3188, 2214, 1725, 1680, 1666, 1472, 1382, 756 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.62 (d, 1H, *J* = 8.45 Hz), 6.74 (d, 1H, *J* = 8.4 Hz), 6.94 (t, 1H, *J* = 7.65 Hz), 7.06 (t, 1H, *J* = 7.65 Hz), 7.15 (t, 1H, *J* = 7.65 Hz), 7.28 (d, 1H, *J* = 7.65 Hz), 7.29 (t, 1H, *J* = 8.4 Hz), 7.67 (d, 1H, *J* = 7.65 Hz), 8.33 (br s, 2H, NH_2, D_2O exchangeable), 10.73 (s, 1H, D_2O exchangeable), 11.18 (s, 1H, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 47.0, 62.6, 62.9, 76.4, 110.4, 111.0, 112.0, 112.7, 115.5, 119.9, 123.0, 123.2, 123.5, 127.1, 127.2, 131.2, 132.2, 143.3, 143.4, 153.9, 173.1, 176.8. MS (*m/z*): 392 (M^+). Anal. Calcd for $C_{22}H_{12}N_6O_2$: C, 67.34; H, 3.08; N, 21.42. Found: C, 67.40; H, 3.04; N, 21.36.
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