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A novel method for the synthesis of functionalized spirocyclic oxindoles by one-pot tandem reaction of vinyl malononitriles with isatylidene malononitriles

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ABSTRACT

One-pot synthesis of novel spirocyclic oxindoles was achieved via vinylogous Michael addition of vinyl malononitriles on isatin–malononitrile adducts as the key step followed by a sequential tandem reaction.

Spirocyclic systems containing one sp^3 carbon atom common to two rings are structurally interesting.[1] The asymmetric structure of the molecule due to the chiral spiro carbon atom is one of the important criteria of the biological activities.[2,3] Among the spirocyclic compounds, the heterocyclic spiro-oxindole framework is an important structural motif in biologically relevant compounds such as natural products and pharmaceuticals.[4] In addition, the oxindole moiety constitutes a key structural element in several natural products,[5] including the antibiotic speradine[6] and the cytostatic welwistatin.[7] Consequently, the development of novel synthetic strategies leading to 3,3-disubstituted oxindole derivatives is of paramount importance. Many synthetic methodologies developed for constructing spirocycles containing 2-oxindole were based on cycloaddition or condensation reactions.[8–15] In continuation of our interest on the synthesis of spirocyclic oxindoles,[16], we herein report a novel method for the synthesis of highly functionalized spirocyclic oxindoles bearing hexahydro naphthalene and tetrahydro indene frameworks by a one-pot, multi-step transformation of vinyl malononitriles with isatylidene malononitriles via vinylogous Michael addition followed by an intramolecular nucleophilic addition and isomerization under mild reaction conditions for the first time.

The Michael addition reaction is widely recognized as one of the most versatile carbon–carbon bond-forming reactions in organic synthesis. Recently, Chen et al. reported that α,α-dicyanoolefin compounds can selectively behave as acceptors[17] or vinylogous donors[18,19] in Michael reactions under easily controllable conditions and yet a simple tertiary amine can smoothly catalyze the Michael addition of an α,α-dicyanoolefin substrate to nitrostyrene by deprotonating the acidic γ-allylic C–H to generate the nucleophilic carbanion.[18a,c] Vinylogous Michael addition was involved as a key step in the synthesis of polysubstituted benzene derivatives from vinyl malononitriles and nitrostyrenes in one-pot tandem reaction.[20] Recently, we reported the Hantzsch ester-promoted reductive cyclization of isatylidene malononitriles to dispiro[cyclopent-3′-ene]bisoxindoles in one-pot method.[21]

From the synthetic point of view, one-pot methods are attractive since they generate less waste, minimize isolation of intermediates in multi-step syntheses of complex molecular targets and save time and cost.[22] With this idea in hand and to contribute in the area of vinylogous Michael addition followed by intramolecular nucleophilic addition, we investigated a series of reactions of vinyl malononitriles with isatylidene malononitriles to obtain spirocyclic oxindoles in a one-pot tandem procedure. Michael-type reactions are reversible and the products formed can often be decomposed to the reactants by heating, and hence we conducted the experiments initially at room temperature.

Our detailed study commenced with the addition of isatylidene malononitrile (**1a**) to the stirred solution of cyclohexanone malononitrile (**2a**) adduct and triethyl amine in ethanol. After 5 min of addition, there is a complete colour change of maroon isatylidene malononitrile forming a clear solution. Monitoring by TLC revealed that the reactants were consumed completely to yield a single product spot. On further stirring for five more minutes, a colourless precipitate was formed which was filtered, washed with 20% EA/PE to afford a pure product (**3a**) in 90% yield (Scheme 1).

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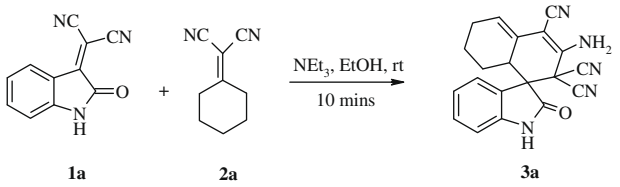
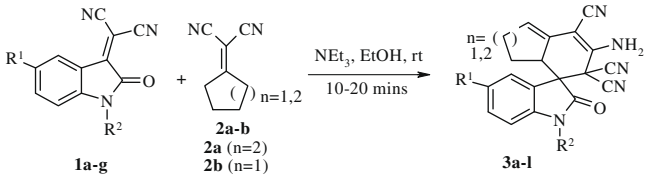


Scheme 1.



Scheme 2.

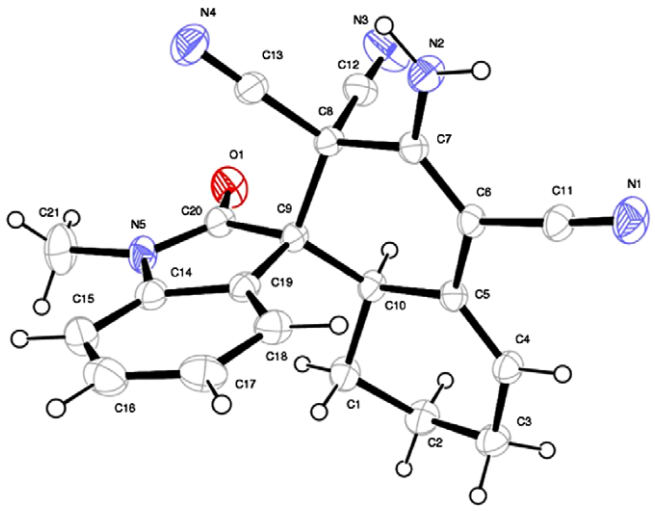


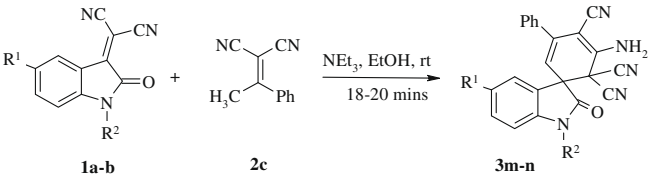
Figure 1. Ortep diagram of **3b**.

The structure of the obtained product (**3a**) was assigned on the basis of spectroscopic data.[23] The peak at 3339 and 3200 cm^{-1} is diagnostic of the primary NH_2 group. In the ^1H NMR, the NH_2 protons resonated at δ 7.51 ppm (exchangeable with D_2O). The structure of the molecule **3b** was further confirmed by single-crystal X-ray data (Fig. 1).[24] To understand the generality of this reaction, we have subjected various isatylidene malononitriles to the reaction of vinyl malononitriles under mild reaction conditions to provide highly functionalized spirocyclic oxindoles in excellent yields (Scheme 2). The results are summarized in Table 1.

Some interesting spirofused cyclohexadienes were achieved with acyclic vinyl malononitriles (**2c**, **2d**) (Scheme 3 and 4). The spirofused cyclohexadienes were purified by column chromatography and were characterized by spectral data.[25] The reaction of acyclic vinyl malononitrile **2d** with **1a**, followed by chromatographic purification resulted in an inseparable mixture of two products **3o**, as major, and **3p**, as minor, in 80:20 ratio as evidenced by ^1H NMR (Scheme 4). Based on the ^1H NMR spectrum with two diastereotopic protons resonating at δ 2.65 and 2.83 ppm as two doublets with geminal coupling constant 16.8 Hz, the olefinic proton resonating at δ 5.68 ppm as quartet and the methyl protons resonating at δ 1.57 ppm as doublet with coupling constant 6.9 Hz, the major product was assigned the structure with exocyclic double bond to the newly formed six-membered ring.

The reactions involving 5-substituted isatylidene malononitriles (**1f** and **1g**) were quite slow compared to the unsubstituted and N-substituted derivatives with cyclic vinyl malononitriles. We also attempted the reaction of vinyl malononitrile with isatin and ethyl cyano acetate adducts. But a mixture of inseparable products was obtained.

A plausible mechanism for the formation of these novel spirocyclic oxindoles is presented in Scheme 5. The first step involves a facile deprotonation of vinyl malononitrile (**2a**) under mild basic conditions to furnish vinylogous carbanion which attacks isatylidene malononitrile (**1a**) followed by an intramolecular nucleophilic addition on CN group resulting in an imine (**5**). The imine on isom-

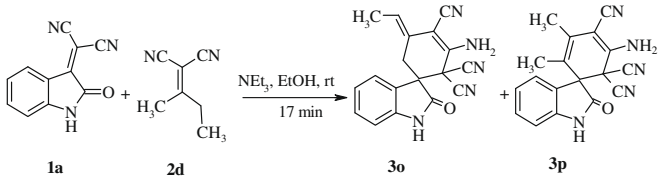


Scheme 3.

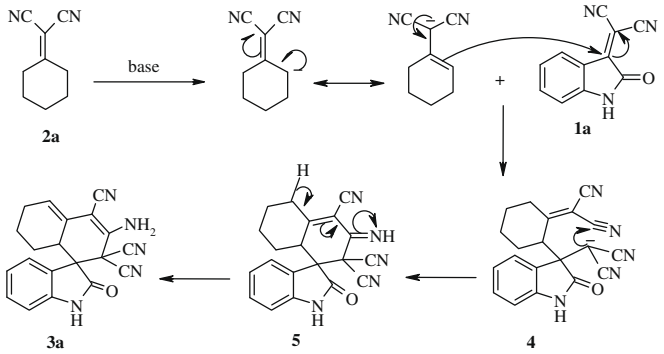
Table 1
Synthesis of spirocyclic oxindoles

Entry	Isatylidene malononitrile			Vinyl malononitrile	Product	Time (min)	Yield[a] (%)
		R^1	R^2				
1	**1a**	H	H	**2a**	**3a**	10	90
2	**1b**	H	Methyl	**2a**	**3b**	12	92
3	**1c**	H	Allyl	**2a**	**3c**	15	90
4	**1d**	H	Propargyl	**2a**	**3d**	13	92
5	**1e**	H	Benzyl	**2a**	**3e**	12	90
6	**1f**	Br	H	**2a**	**3f**	20	85
7	**1g**	NO_2	H	**2a**	**3g**	22	83
8	**1a**	H	H	**2b**	**3h**	15	90
9	**1b**	H	Methyl	**2b**	**3i**	13	90
10	**1c**	H	Allyl	**2b**	**3j**	15	88
11	**1d**	H	Propargyl	**2b**	**3k**	13	91
12	**1f**	Br	H	**2b**	**3l**	19	84
13	**1a**	H	H	**2c**	**3m**	20	78
14	**1b**	H	Methyl	**2c**	**3n**	18	81
15	**1a**	H	H	**2d**	**3o, 3p**	17	75[b]

[a] Isolated yield.
[b] Isolated as a mixture of **3o** and **3p**.



Scheme 4.



Scheme 5. Plausible mechanism.

erization yielded the corresponding spirocyclic oxindole (**3a**) in one-pot, sequential transformation.

During the course of our investigations, we have observed that the reaction of isatylidene malononitrile with cyclic vinyl malononitriles (**2a**, **2b**) furnishes exocyclic double bond in the newly formed six-membered ring, whereas the double bond is endocyclic when acylic vinyl malononitrile (**2c**) is used.

Several advantages of this method like milder reaction condition, shorter reaction time, high yield, simple experimental and isolation procedures make it an efficient route for the synthesis of novel spirocyclic oxindoles.

In summary, we have demonstrated a novel method for the synthesis of functionalized spirocyclic oxindoles via vinylogous Michael addition followed by a sequential intramolecular addition and isomerization reaction in one-pot, tandem procedure.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.082.

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23. *General procedure for the synthesis of spirocyclic oxindole* (**3a**): To a stirred solution of 1 mmol of cyclohexanone malononitrile adduct (**2a**) and NEt_3 (20 mmol %) in ethanol at room temperature, 1 mmol of isatylidene malononitrile (**1a**) was added and continued stirring for about 10 min to form a colourless precipitate. After the reaction was complete as indicated by TLC, the precipitate was filtered and washed with 20% ethyl acetate/pet ether to afford pure product (**3a**) as off-white solid in 90% yield.
Spectral data of spiro oxindole **3a** (Table 1): Off-white solid. Yield: 90%, mp 238–240 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.42 (q, 1H, J = 12.2 Hz), 1.41 (m, 1H), 1.52 (m, 1H), 1.59 (m, 1H), 1.86 (m, 1H), 2.05 (m, 1H,), 2.86 (d, 1H, J = 10.7 Hz), 5.88 (m, 1H,), 6.83 (d, 1H, J = 7.65 Hz), 6.97 (d, 1H, J = 7.65 Hz), 7.02 (t, 1H, J = 7.65 Hz), 7.34 (t, 1H, J = 7.65), 7.51 (s, 2H, D_2O exchangeable), 11.35 (s, 1H, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6) δ: 20.7, 23.9, 25.0, 37.4, 42.6, 55.0, 82.0, 111.1(2C), 111.2, 116.0, 122.9, 123.4, 124.2, 125.4, 125.9, 131.4, 142.8, 143.3, 173.7. IR ν_{max} (KBr) : 3339, 3200, 2934, 2216, 1733, 1614, 619 cm^{-1}. Mass (ESI): 342 (M+1). Anal. Calcd for $C_{20}H_{15}N_5O$: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.31; H, 4.36; N, 20.47.
24. Crystallographic data for compound **3b** in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC 749095. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).
25. *General procedure for the synthesis of spirocyclic oxindole* (**3m**): To a stirred solution of 1 mmol of acetophenone malononitrile adduct (**2c**) and NEt_3 (20 mmol %) in ethanol at room temperature, 1 mmol of isatylidene malononitrile (**1a**) was added and continued stirring for the time mentioned in Table 1. After the reaction was complete as indicated by TLC, the solvent was evaporated and the crude product was purified by column chromatography (30% ethyl acetate/pet ether) to afford product (**3m**). The same procedure was followed for **3o** and **3p** also.
Spectral data of spiro oxindole **3m** (Table 1):
Brown solid. Yield: 78%, mp 230–232 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.52 (s, 1H,), 6.98 (d, 1H, J = 7.6 Hz), 7.08 (t, 1H, J = 7.65 Hz), 7.35 (m, 7H), 8.22 (s, 2H, D_2O exchangeable) 11.25 (s, 1H, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6) δ: 43.9, 54.7, 77.1, 111.1, 111.3, 112.2, 123.7, 124.6, 131.7, 137.1, 139.3, 148.5, 173.4. IR ν_{max} (KBr) : 3410, 3301, 3196, 2213, 1725, 1643, 799. Mass (ESI): 364 (M+1). Anal. Calcd for $C_{22}H_{13}N_5O$: C, 72.72; H, 3.61; N, 19.27. Found: C, 72.67; H, 3.55; N, 19.21.