Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1506

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COMMUNICATION

Efficient synthesis of multicyclic spirooxindoles *via* a cascade Michael/Michael/oxa-Michael reaction of curcumins and isatylidene malononitriles†‡

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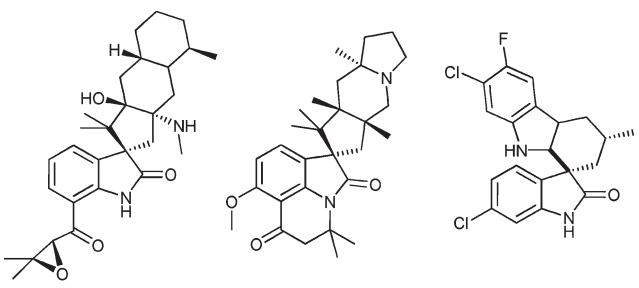
Received 28th November 2011, Accepted 5th December 2011
DOI: 10.1039/c2ob06995d

A cascade Michael/Michael/oxa-Michael reaction between curcumins and isatylidene malononitriles has been developed. Multicyclic spirooxindoles were prepared in excellent yields and diastereoselectivities. DMAP was found to catalyze this transformation efficiently under mild reaction conditions.

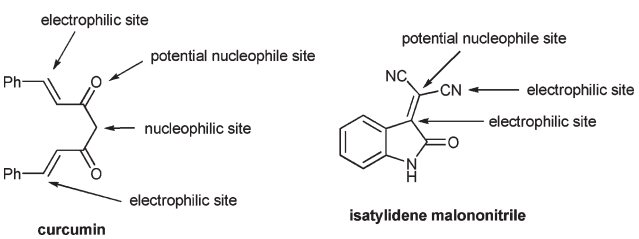
Multicyclic spirooxindoles are found in a range of natural products. Many of them, such as cycloplamine, strychnofoline and NITD609, possess interesting biological activities (Scheme 1).[1] Cycloplamine B was found to inhibit the growth of androgen-independent prostate cancer cells.[2] Strychnofoline isolated from the leaves of *Strychnos usambarensis*, showed potent antitumor activity.[3] NITD609 may have potential therapeutic use for malaria.[4] Extensive efforts have been made to develop synthetic methods of multicyclic spirooxindole scaffolds.[5] The cascade reactions based on 3-methyleneindolinone and other indolinone derivatives are extremely attractive in terms of efficiency and atomic economy.[6,7] Barbas III and co-workers developed a cascade Michael/aldol reaction of 3-substituted oxindoles and 3-methyleneindolinones. Bis-spirooxindoles were prepared in good yields and enantioselectivities.[7a] Chen and co-workers reported the enantioselective synthesis of bicyclic spirooxindoles *via* a cascade Michael/Michael/Michael/aldol reaction from 3-methyleneindolinones and enals.[7b] Other examples include the Michael/Michael reaction of 3-methyleneindolinones and enones,[7c] Michael/Michael/aldol reaction of 3-methyleneindolinones, aldehydes and enals,[7d] Michael/intramolecular cyclization of methyleneindolinones and α-isothiocyanato imides,[7e] Michael/aldol reaction of 3-acyl-indolinones and enones,[7f] double Michael/aldol reaction of indolinones and enals,[7g] aza-Michael/intramolecular cyclization of methyleneindolinones and α-bromoacetamides.[7h]

In recent years, we have been interested in the organocatalytic synthesis of cyclic products *via* cascade/domino reactions.[8] We envision that curcumin, which is readily available from the spice turmeric, is a valuable multi-functional nucleophile for cascade reactions (Scheme 2).[9] Recently Ye and co-workers reported the organocatalytic asymmetric conjugate addition of curcumins to nitroalkenes.[10] Namboothiri and co-workers developed cascade reactions of curcumins with nitroalkenes and α-bromonitroalkenes. Highly functionalized cyclohexanones and dihydrofurans were obtained in good yields and diastereoselectivities.[11] Despite these efforts, the full potential of curcumins as multi-functional nucleophiles for cascade reactions remains to be explored. In this paper, we report an efficient cascade reaction of curcumins and isatylidene malononitriles (Scheme 2). Multicyclic spirooxindoles were prepared in excellent yields and diastereoselectivities.

The reaction of isatylidene malononitrile **1a** and curcumin **2a** was examined in ethanol at room temperature. A number of bases were used as the catalyst. Multicyclic spirooxindoles **3a**/**3a′** were obtained and the results are summarized in Table 1.



Scheme 1 Multicyclic spirooxindoles with interesting biological activities.



Scheme 2 Curcumins and isatylidene malononitriles as multifunctional substrates.

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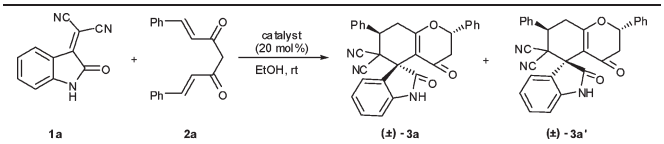
† This article is part of the joint *ChemComm–Organic & Biomolecular Chemistry* 'Organocatalysis' web themed issue.

‡ Electronic supplementary information (ESI) available. CCDC reference number 847692. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06995d

Table 1 Screening of catalysts[a]



Entry	Catalyst	dr[b]	Time (h)	Yield (%)[c]
1	NaOH	60/40	24	23
2	K_2CO_3	70/30	24	28
3	ET_3N	89/11	18	86
4	DABCO	88/12	18	93
5	DMAP	91/9	18	98
6	Pyrrolidine	86/14	16	92
7	Piperidine	85/15	16	90
8	*N*-methylpyrrolidine	91/9	40	82
9	*N*-methylmorpholine	89/11	40	60
10	Pyridine	67/33	40	10

[a] The reactions were carried out with **1a** (0.05 mmol), **2a** (0.05 mmol) and catalyst (0.01 mmol) in EtOH (1 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Isolated yields after column chromatography.

Inorganic bases, such as NaOH and K_2CO_3 resulted in low yields and diastereoselectivities (Table 1, entries 1 and 2). Organic bases including Et_3N, DABCO, DMAP, pyrrolidine, piperidine, *N*-methylpyrrolidine and *N*-methylmorpholine provided **3a** in good yields and diastereoselectivities (Table 1, entries 3–9). DMAP was preferred in terms of the yield and diastereoselectivity (Table 1, entry 5). Less basic pyridine is inefficient for this reaction (Table 1, entry 10).

The effect of reaction solvent was also studied and the results are summarized in Table 2. A low yield was obtained in hexane due to poor solubility of isatylidene malononitrile (Table 2, entry 1). Good yields and moderate diastereoselectivities were achieved in toluene, CH_2Cl_2, $CHCl_3$, THF, AcOEt and CH_3CN (Table 2, entries 2–7). The non-protonic polar solvent DMF gave a poor yield of **3a** (Table 2, entry 8). Alcohols are more suitable solvents for the reaction (Table 2, entries 9–11). Ethanol was preferred in terms of the yield and diastereoselectivity. The reaction was also examined at 0 °C, however only a low yield was obtained. Isatylidene malononitrile is not fully soluble at this temperature in ethanol.

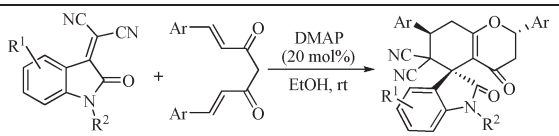
The scope of reaction substrates was examined and the results are summarized in Table 3. Isatylidene malononitriles with substitutions (5-MeO, 6-Cl and 7-Br) at the phenyl ring provided the products in good yields and diastereoselectivities (Table 3, entries 2–4). 6-MeO substituted isatylidene malononitrile showed lower reactivity and moderate yield was obtained (Table 3, entry 5). The introduction of *N*-methyl or *N*-benzyl exerted small influence on the yield and diastereoselectivity (Table 3, entries 6 and 7). Curcumins bearing both electron-donating and electron-withdrawing groups afforded the products in good yields and diastereoselectivities (Table 3, entries 8–11). The 2,5-di-MeO substituted substrate also gave a good result (Table 3, entry 12). The reaction is applicable for heteroaryl derivatives of curcumin (Table 3, entries 13 and 14), however low diastereoselectivity was observed for the thienyl derivative (Table 3, entry 14). On the other hand, the reaction of isatylidene malonate and isatylidene cyanoacetate with curcumin did not occur under the present reaction conditions. Their lower electrophilic reactivity may account for the result. The reaction of isatylidene nitromethane with curcumin did not generate the desired multicyclic spirooxindoles, instead partially polymerization of isatylidene nitromethane was observed.

Table 2 Effect of reaction solvents[a]

Entry	Solvent	dr	Time (h)	Yield (%)
1	Hexane	80/20	72	21
2	Toluene	76/24	72	84
3	CH_2Cl_2	78/12	72	80
4	$CHCl_3$	71/29	72	81
5	THF	76/24	72	82
6	AcOEt	71/29	18	80
7	CH_3CN	85/15	18	88
8	DMF	87/13	18	20
9	*i*-PrOH	87/13	18	93
10	MeOH	86/14	18	94
11	EtOH	91/9	18	98
12[b]	EtOH	88/12	144	11

[a] The reactions were carried out with **1a** (0.05 mmol), **2a** (0.05 mmol) and DMAP (0.01 mmol) in solvent (1 mL) at room temperature. [b] The reaction was carried out at 0 °C.

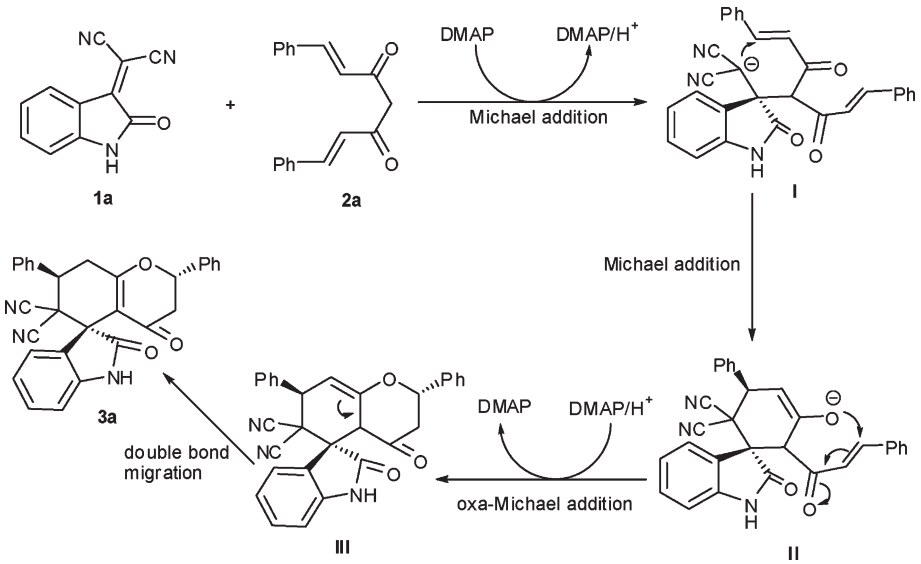
Table 3 Cascade reaction of isatylidene malononitriles and curcumins[a]



Entry	R^1	R^2	Ar	dr[b]	Time (h)	Yield (%)[c]
1	H	H	Ph	91/9	18	**3a**, 98
2	5-MeO	H	Ph	91/9	18	**3b**, 92
3	5-Cl	H	Ph	91/9	18	**3c**, 90
4	7-Br	H	Ph	89/11	18	**3d**, 94
5	6-MeO	H	Ph	88/12	40	**3e**, 53
6	H	Me	Ph	92/8	18	**3f**, 94
7	H	Bn	Ph	88/12	18	**3g**, 91
8	H	H	4-MeO-C_6H_4	89/11	18	**3h**, 92
9	H	H	4-Cl-C_6H_4	95/5	18	**3i**, 99
10	H	H	2-MeO-C_6H_4	88/12	18	**3j**, 89
11	H	H	2-Cl-C_6H_4	83/17	18	**3k**, 92
12	H	H	2,5-Di-MeO-C_6H_3	88/12	24	**3l**, 87
13	H	H	2-Furanyl	86/14	18	**3m**, 91
14	H	H	2-Thienyl	75/25	18	**3n**, 97

[a] The reactions were carried out with **1a–1g** (0.05 mmol), **2a–2h** (0.05 mmol), DMAP (0.01 mmol) in EtOH (1 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Isolated yields after column chromatography.

The relative configuration of **3a** was determined by X-ray diffraction analysis (Fig. 1).[12] The configuration of minor diastereoisomer **3a′** was suggested based on its ^{1}H NMR and NOESY analysis. The relative configurations of products **3b–3n** were assigned analogously.



Scheme 3 Plausible reaction mechanism.

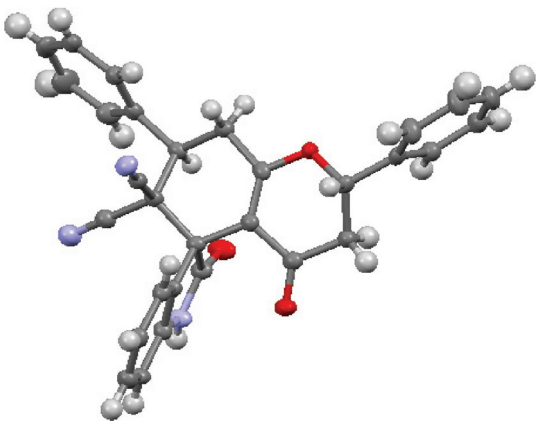
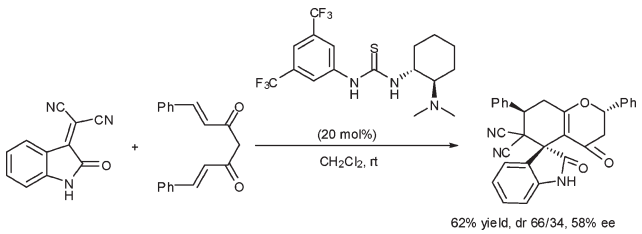


Fig. 1 X-ray crystal structure of **3a**.



Scheme 4 Asymmetric reaction of isatylidene malononitrile and curcumin.

A plausible reaction mechanism is proposed in Scheme 3. DMAP removes a proton from curcumin **2a** to generate an enol anion. It attacks isatylidene malononitrile **1a** and the resulting malononitrile anion **I** undergoes an intramolecular conjugate addition. The enol anion **II** is formed and subsequently takes part in an oxa-Michael reaction. A proton is transferred from DMAP/H^+ to provide intermediate **III**. The product **3a** is formed after a migration of the double bond in the intermediate **III**.

An asymmetric version of this reaction was studied using Takemoto's amine-thiourea as the catalyst, but only moderate yield and low enantioselectivity were achieved (Scheme 4).[13,14]

In conclusion, we have developed an efficient synthesis of multicyclic spirooxindoles from readily available isatylidene malononitriles and curcumins. Curcumins work as multifunctional nucleophiles and electrophiles in this transformation. A reaction mechanism of cascade Michael/Michael/oxa-Michael addition and double bond migration is proposed. Further development of highly enantioselective version of this reaction is currently under investigation.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 20972195, 21172270), Natural Science Foundation of Guangdong (No. 8451008901000380) and Fundamental Research Funds for the Central Universities is gratefully acknowledged.

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