ORGANIC LETTERS

2012
Vol. 14, No. 5
1274–1277

N-Heterocyclic Carbene-Catalyzed Three-Component Domino Reaction of Alkynyl Aldehydes with Oxindoles

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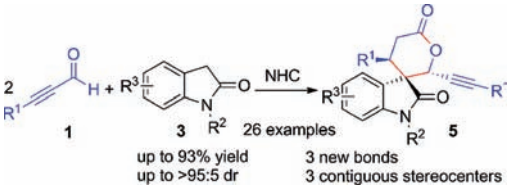
Received January 19, 2012

ABSTRACT



A new and stereoselective synthetic approach to spirooxindole 4*H*-pran-2-one derivatives with three contiguous stereogenic centers has been developed via an NHC-catalyzed three-component domino reaction of alkynyl aldehydes with oxindoles. The reaction proceeds smoothly in good yields with good to high diastereoselectivities. These novel heterocyclic spirooxindoles may provide promising candidates for drug discovery. Additionally, a possible mechanism for the entire reaction sequence is proposed.

The spirooxindoles are structurally interesting and frequently present as important substructures in a broad range of complex natural products, pharmaceuticals, and synthetic heterocycles with highly pronounced biological activities.[1] A potentially promising subset of these bioactive compounds is the oxa-spirooxindoles.[2] As a particular class of oxa-spirooxindoles, the spirooxindole 4*H*-pyran-2-ones are characterized by a spiro fusion to the 4*H*-pyran-2-one ring which is a valuable subunit of many bioactive natural products[3] at the 3-position of the oxindole core. However, few investigations have been focused on the spirooxindole 4*H*-pyran-2-ones, and versatile approaches to this unique heterocyclic motif are considerably limited.[4] Thus, the search for general and efficient methods for the synthesis of spirooxindole 4*H*-pyran-2-ones is highly desirable.

The highly efficient construction of complex skeletons of molecules with potential biological activities by domino

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(3) For selected examples, see: (a) de Lemos, E.; Agouridas, E.; Sorin, G.; Guerreiro, A.; Commerçon, A.; Pancrazi, A.; Betzer, J.-F.; Lannou, M.-I.; Ardisson, J. *Chem.—Eur. J.* **2011**, *17*, 10123. (b) Smith, A. B.; Sugasawa, K.; Atasoylu, O.; Yang, C.-P. H.; Horwitz, S. B. *J. Med. Chem.* **2011**, *54*, 6319. (c) Chaturvedi, D.; Goswami, A.; Saikia, P. P.; Barua, N. C.; Rao, P. G. *Chem. Soc. Rev.* **2010**, *39*, 435.

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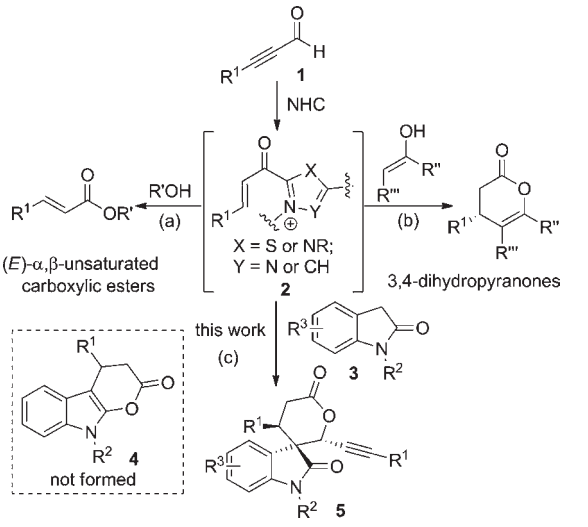
(5) For selected reviews, see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (b) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092. (c) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (d) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341.

10.1021/ol300148f
Published on Web 02/21/2012

reactions has drawn much attention over the past decade.[5] In recent years, N-heterocyclic carbenes (NHCs) have also evoked considerable interest because of their wide-ranging utility as efficient organocatalysts in a large number of umpolung transformations of different types of aldehdyes.[6] However, few efforts have been focused on the α,β-unsaturated ynals **1** (namely alkynyl aldehydes),[7] which are an important source of catalytically generated α,β-unsaturated acyl azolium **2** (Scheme 1),[8] a fascinating reactive intermediate in a rapidly growing number of transformations mediated by NHCs. Zeitler[7a,b] has reported the pioneering work of an NHC-promoted stereoselective redox esterification of alkynyl aldehydes **1** providing (*E*)-configurated α,β-unsaturated carboxylic esters (Scheme 1, reaction a). Bode[7c] and Xiao[7d,e] have recently described the NHC-catalyzed reaction of alkynyl aldehydes **1** with various enols to give functionalized 3,4-dihydropyranones (Scheme 1, reaction b). Inspired by these results and as part of our ongoing program to explore efficient methodologies for chemical transformations using NHCs as organocatalysts,[9] we envisioned that the combination of alkynyl aldehydes **1** and oxindoles **3** in the presence of NHCs may produce indole-fused dihydropyranones **4**.[10] Interestingly, instead of the anticipated products **4**, the spirooxindole 4*H*-pyran-2-ones **5** with three contiguous stereogenic centers were obtained in good yields with good to high diastereoselectivities via a three-component domino process (Scheme 1, reaction c).[11] This strategy offered an efficient and stereoselective access to the construction of highly functionalized spirooxindole 4*H*-pyran-2-ones which may provide promising candidates for drug discovery. Herein, we wish to report our recent results.

Scheme 1. NHC-Catalyzed Reactions of Alkynyl Aldehydes **1**



At the outset of our studies, a set of experiments were carried out to evaluate and optimize the conditions for the reaction of alkynyl aldehydes with oxindoles (Table 1). Initially, we examined the model reaction of 3-phenylpropioaldehyde **1a** (3.0 equiv) with oxindole **3a** (1.0 equiv) in the presence of carbene precursors **A**−**F** (entries 1−3). NHCs derived from precursors **A**−**E** proved unsuitable for this reaction, leading to the formation of a large quantity of Knoevenagel product **6a** (entries 1 and 2). Surprisingly, with 30 mol % of imidazolium salt **F** and 30 mol % of DBU in THF, spirooxindole 4*H*-pyran-2-one **5a** was obtained in an 54% yield with modest diastereoselectivity which was accompanied by <15% of isolated Knoevenagel product **6a** (entry 3). The product **5a** was constructed from one molecule of **3a** and two molecules of **1a** via a three-component domino process. Further screening of various bases suggested *t*-BuOK was the optimal one (entries 4−8). The attempts to decrease the catalyst loading led to decreased yields and a prolonged reaction time (entries 9 and 10). Moreover, the examination of several solvents such as PhMe, DCE, DMF, and 1,4-dioxane also did not improve the yield. Unfortunately, in all cases, the Knoevenagel product **6a** could not be suppressed completely. So, the optimal reaction conditions were established as follows: 30 mol % of catalyst **F** and 30 mol % of *t*-BuOK in THF for 2 h at 65 °C with an 60% yield and 85:15 dr (entry 8). The structure and relative stereochemistry of the products were established by spectroscopic analysis and further confirmed by X-ray crystallography of **5a**.[12]

With the optimized conditions in hand, the generality of the reaction was explored (Table 2). We found that the reaction could accommodate a broad range of substituted oxindoles, although the Knoevenagel products were also isolated in <15% yields in most cases (entries 1−13). Oxindoles **3a**−**d** with different N-protecting groups had

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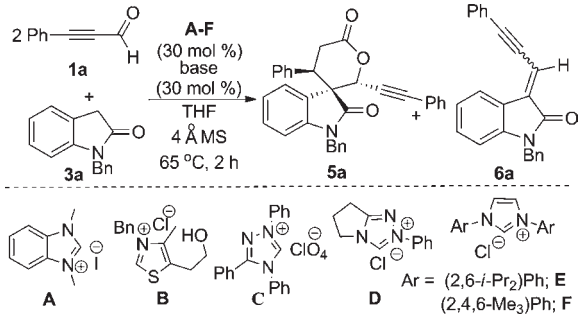
(12) See Supporting Information for details.

Table 1. Optimization of Reaction Conditions[a]

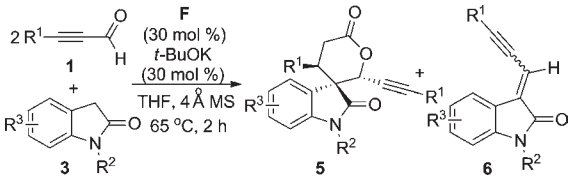


entry	catalyst	base	yield[b] (%)		dr of **5a**[c]
			5a	**6a**	
1	**A-D**	DBU	0	quant	—
2	**E**	DBU	trace	quant	—
3	**F**	DBU	54	<15	60:40
4	**F**	K_2CO_3	55	<15	78:22
5	**F**	Cs_2CO_3	46	<15	80:20
6	**F**	Et_3N	49	<15	81:19
7	**F**	DIPEA	47	<15	76:24
8	**F**	***t*-BuOK**	**60**	**<15**	**85:15**
9[d]	**F**	*t*-BuOK	48	<15	86:14
10[e]	**F**	*t*-BuOK	45	<15	85:15

[a] All reactions were performed by using 3.0 equiv of **1a** (0.6 mmol), 1.0 equiv of **3a** (0.2 mmol), in the presence of 4 Å MS (100 mg), 30 mol % of a carbene precursor, and 30 mol % of a base in THF (3 mL) at 65 °C under N_2 for 2 h. [b] Isolated yield based on **3a**. [c] Diastereomeric ratio determined by H^1 NMR of the crude product. [d] The reaction was carried out with 20 mol % of **F** and 20 mol % of *t*-BuOK for 5 h, and 15% of **3a** was recovered . [e] The reaction was carried out with 30 mol % of **F** and 20 mol % of *t*-BuOK for 5 h, and 18% of **3a** was recovered.

no significant impact on the yields and diastereoselectivities (entries 1−4). Remarkably, N-unprotected oxindole **3e** could also give desired product **5e** in a ratio of >95:5, although the yield was lower and 22% of **3e** was recovered (entry 5). Oxindoles with electron-withdrawing groups (F, Cl, Br) and an electron-donating group (Me) at the 4-, 5-, 6-, or 7-position worked equally well to afford the desired products in good yields with good to high diastereoselectivities (entries 6−13). Subsequently, a variety of alkynyl aldehydes **1** were tested for this domino reaction with oxindole **3g** (entries 14−24). The reaction also proceeded smoothly for alkynyl aldehydes **1b**−**i** with various substituents at different positions on the phenyl ring, affording the corresponding products in good yields with good to high diastereoselectivities except 3-Cl substituted substrate **1f** and 2,3-disubstituted substrate **1i** (entries 14−21). Unfortunately, in the case of 3-(1-naphthyl)propiolaldehyde **1j**, no desired spirooxindole product was obtained, while 35% of Knoevenagel product was isolated and 38% of **3g** was recovered (entry 22). It was noteworthy that 3-heteroaromatic-substituted alkynyl aldehyde **1k** was also subjected to this process (entry 23). 3-Aliphatic-substituted alkynyl aldehyde **1l** was then examined, resulting in quantitative formation of the Knoevenagel product without any desired product (entry 24). Finally, this reaction pattern was further applied to N-unprotected oxindole **3n** (entries

Table 2. Scope of the Reaction between Alkynyl Aldehydes **1** and Oxindoles **3**[a]



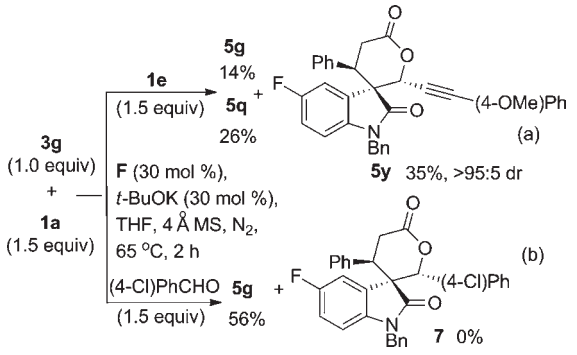
entry	R^1, **1**	R^2, R^3, **3**	**5**	yield[b] (%)		dr of **5**[c]
				5	**6**	
1	Ph, **a**	Bn, H, **a**	**a**	60	<15	85:15
2	Ph, **a**	allyl, H, **b**	**b**	60	<15	86:14
3	Ph, **a**	Me, H, **c**	**c**	63	<15	88:12
4	Ph, **a**	acyl, H, **d**	**d**	61	<15	90:10
5[d]	Ph, **a**	H, H, **e**	**e**	40	<15	>95:5
6	Ph, **a**	Bn, 4-Cl, **f**	**f**	75	<15	>95:5
7	Ph, **a**	Bn, 5-F, **g**	**g**	88	<10	88:12
8	Ph, **a**	Bn, 5-Cl, **h**	**h**	61	<15	94:6
9	Ph, **a**	Bn, 5-Br, **i**	**i**	64	<15	94:6
10	Ph, **a**	Bn, 5-Me, **j**	**j**	69	<15	93:7
11	Ph, **a**	Bn, 6-Cl, **k**	**k**	82	<10	95:5
12	Ph, **a**	Bn, 7-Cl, **l**	**l**	75	<15	>95:5
13	Ph, **a**	Bn, 7-Me, **m**	**m**	64	<15	88:12
14	(4-F)Ph, **b**	Bn, 5-F, **g**	**n**	61	<15	91:9
15	(4-Cl)Ph, **c**	Bn, 5-F, **g**	**o**	64	<15	85:15
16	(4-Me)Ph, **d**	Bn, 5-F, **g**	**p**	74	<15	93:7
17	(4-OMe)Ph, **e**	Bn, 5-F, **g**	**q**	93	<5	>95:5
18	(3-Cl)Ph, **f**	Bn, 5-F, **g**	**r**	46	32	>95:5
19	(3-Me)Ph, **g**	Bn, 5-F, **g**	**s**	66	<15	>95:5
20	(2-Cl)Ph, **h**	Bn, 5-F, **g**	**t**	82	<10	>95:5
21[e]	(2,3-OMe_2)Ph, **i**	Bn, 5-F, **g**	**u**	50	<15	>95:5
22[f]	1-naphthyl, **j**	Bn, 5-F, **g**	—	0	35	—
23	2-furyl, **k**	Bn, 5-F, **g**	**v**	61	<15	>95:5
24	Ph(CH_2)$_2$, **l**	Bn, 5-F, **g**	—	0	quant	—
25	Ph, **a**	H, 5-F, **n**	**w**	60	<15	>95:5
26	(4-OMe)Ph, **e**	H, 5-F, **n**	**x**	91	<5	>95:5

[a] All reactions were performed by using 3.0 equiv of **1** (0.6 mmol), 1.0 equiv of **3** (0.2 mmol) in the presence of 30 mol % of **F** and 30 mol % of *t*-BuOK in THF (3 mL) at 65 °C under N_2 for 2 h. [b] Isolated yield based on **3**. [c] Diastereomeric ratios determined by H^1 NMR of the crude products. [d] 22% of **3e** was recovered. [e] 20% of **3g** was recovered. [f] 38% of **3g** was recovered.

25 and 26). It was found that the reaction of **3n** with alkynyl aldehydes **1a** and **1e** respectively gave the corresponding products in significantly increased yields compared to N-unprotected oxindole **3e**.

To further explore the scope of the reaction, we paid attention to the development of three-component couplings with two different aldehydes (Scheme 2). We selected the reaction of oxindole **3g** with alkynyl aldehydes **1a** and **1e** to examine the possibility of this three-component coupling. It was interesting that, among four possible coupling products, products **5g** and **5q** were obtained in 14% and 26% yields respectively, while only one product **5y** derived from the cross-coupling of **3g** with **1a** and **1e** was obtained in an 35% yield (reaction a). The structure of **5y** was established by COSY, HSQC, and HMBC analysis.[12] The reaction was then tested by using oxindole **3g**, alkynyl aldehyde **1a**, and 4-chlorobenzaldehyde. Neverthless, only product **5g** was isolated in an 56% yield, and product **7** from the coupling of

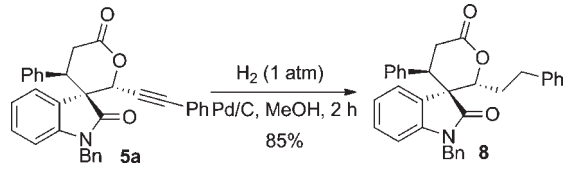
Scheme 2. Three-Component Couplings with Two Different Aldehydes



3g with **1a** and 4-cholorobenzaldehyde was not obtained, perhaps due to the lower electrophilicity of 4-cholorobenzaldehyde vs alkynyl aldehyde **1a** (reaction b).

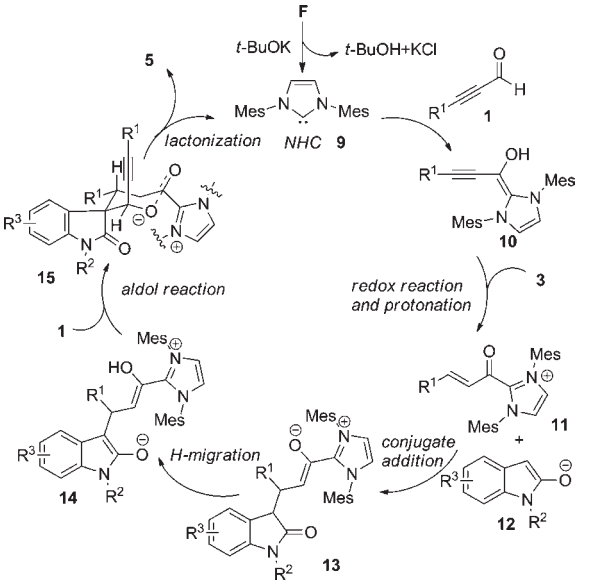
The resulting highly functionalized spirooxindoles offer many opportunities for chemical transformations. For example, the reduction of alkynyl group of **5a** with H_2−Pd/C gave hydrogenated product **8** in an 85% yield (Scheme 3).

Scheme 3. Hydrogenation of Compound **5a**



A mechanistic rationalization for this unexpected domino reaction is proposed as shown in Scheme 4. The domino process initiates with the addition of NHC **9** generated upon deprotonation of carbene precursor **F** with *t*-BuOK to alkynyl aldehydes **1**, affording the Breslow intermediate **10**.[7] After a subsequent redox reaction and protonation with the acidic H-donor, oxindoles **3**, α,β-unsaturated acyl azolium **11**, and intermediate **12** are formed. The direct conjugate addition of **12** to **11** followed by H-migration gives adduct **14**, which subsequently undergoes domino intermolecular aldol reaction with another molecule of alkynyl aldehydes **1** and lactonization to deliver products **5** and regenerates NHC **9** for the next catalytic cycle. The stereochemistry of the products may be rationalized by the chair-transition state **15** in the process of lactonization. Steric hindrance leads to an anti-orientation

Scheme 4. Proposed Mechanism for NHC-Catalyzed Reaction between Oxindoles and Alkynyl Aldehydes



of the C≡C—R^1 group and the carbonyl of oxindole. Another R^1 group is relatively large, so it should also be in an anti-orientation to the C≡C—R^1 group to avoid conflict with the latter.

In conclusion, we have described an NHC-catalyzed three-component domino reaction of oxindoles with alkynyl aldehydes, which offers an effective and stereoselective strategy for the synthesis of highly functionalized spirooxindole 4*H*-pyran-2-ones with three contiguous stereogenic centers from easily accessible materials. The unique structure of these products may be attractive for potential drug discovery. Research on an enantioselective synthesis of this protocol as well as exploration of novel NHC-catalyzed reactions of alkynyl aldehydes is currently underway.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 21002124, 30973609), Specialized Research Fund for the Doctoral Program of Higher Education of China (No. 20100096120009), and the Project Program of State Key Laboratory of Natural Medicines of China Pharmaceutical University (No. JKGQ201101) for financial support.

Supporting Information Available. Experimental procedures, compound characterization, and X-ray data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.