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Expedient and Divergent Tandem One-Pot Synthesis of Benz[*e*]indole and Spiro[indene-1,3′-pyrrole] Derivatives from Alkyne-Tethered Chalcones/Cinnamates and TosMIC

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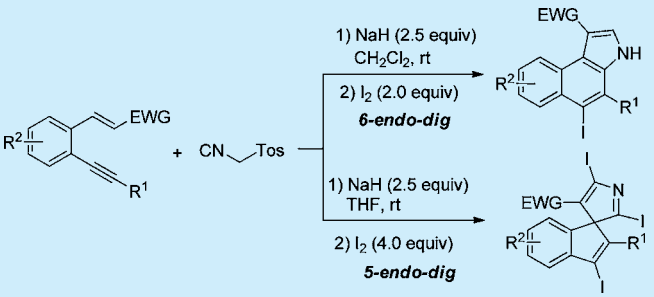
Supporting Information

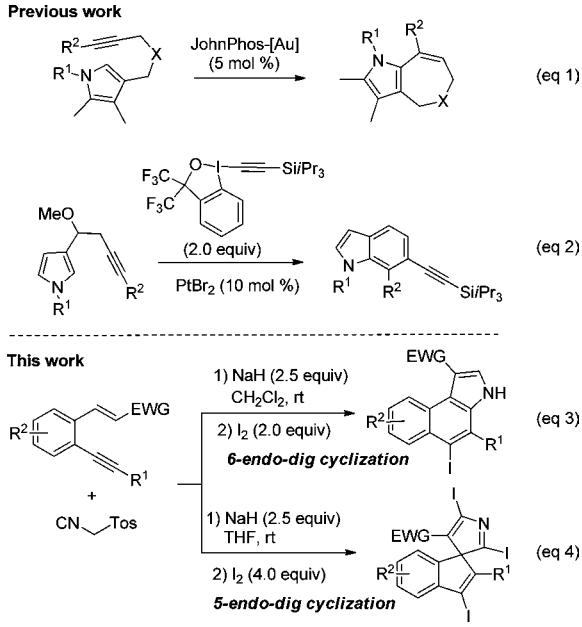
ABSTRACT: An efficient solvent-dependent regioselective [3 + 2]-cycloaddition/iodocyclization cascade reaction of alkyne-tethered chalcones/cinnamates and TosMIC has been developed. The reaction represents a novel protocol for the expedient and divergent one-pot synthesis of benz[*e*]indoles and spiro[indene-1,3′-pyrroles] from acyclic common precursors at room temperature.



Divergent tandem one-pot synthesis has attracted significant attention in chemical synthesis because it can provide quick access to structurally diversified architectures from the same common starting materials.[1] In this context, isocyanides are promising candidate substrates in divergent tandem reactions owing to their controllable multiple reactivities under carefully selected reaction conditions.[2] In 2005, Yamamoto and co-workers reported the catalyst-dependent divergent synthesis of 2,3-di-EWG- and 2,4-di-EWG-substituted pyrroles from [3 + 2]-cycloaddition of isocyanoacetates with electron-deficient alkynes.[3] Recently, we reported a regioselective tandem heterocyclization of isocyanoacetate with alkenoylacetamides for the divergent synthesis of C_2-tethered pyrrole/oxazole pairs[4] and 7-azatetrahydroindoles,[5] as well as a regiodivergent tandem synthesis of 2,3,5-trisubstituted pyrroles from isocyanoacetate and α-formyl ketene dithioacetals.[6] Despite the research efforts, the activated methylene isocyanides participating in divergent tandem reactions for the rapid assembly of molecular complexity are still limited.

Recently, the intramolecular electrophilic cyclization of alkynes with pyrroles was recognized as a powerful tool for the preparation of annulated pyrrole derivatives.[7] In 2014, Wan and co-workers reported elegant gold(I)-catalyzed[8] intramolecular alkenylations of β-ynepyrroles for the synthesis of fused cycloheptapyrroles (Scheme 1, eq 1).[7a] This year, Waser and co-workers reported a novel Pt-catalyzed domino reaction with benziodoxole reagents from alkyne-tethered pyrroles for accessing benzene-alkynylated indoles (Scheme 1, eq 2).[7b] However, in these transformations the preformed pyrroles were usually used as starting materials.[7] As part of our continuing interest in the heterocyclization of isocyanides,[9] we herein report an expedient and divergent tandem one-pot synthesis of benz[*e*]indole[10] and spiro[indene-1,3′-pyrrole] derivatives from alkyne-tethered chalcones/cinnamates[11] and tosylmethyl isocyanide (TosMIC) (Scheme 1, eqs 3 and 4). This one-pot reaction involves a [3 + 2]-cycloaddition and iodocyclization cascade and provides a novel protocol for the efficient and regioselective synthesis of fused- and spiro-pyrrole derivatives

Scheme 1. Intramolecular Electrophilic Cyclization of Alkynes with Pyrroles



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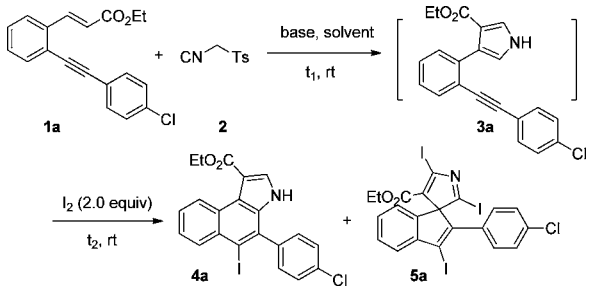
from the acyclic starting materials. To our knowledge, this is the first example of intramolecular electrophilic cyclization of alkynes with *in situ* generated pyrroles.

Initially, the one-pot tandem reaction of alkyne-tethered cinnamate **1a** with TosMIC **2** was employed to screen the reaction conditions. As shown in Table 1, when a mixture of cinnamate **1a** and TosMIC **2** (2.0 equiv) was treated with NaH (2.5 equiv) at room temperature for 8 h in CH_2Cl_2, the pyrrole intermediate **3a** was formed (detected by TLC), then I_2 (2.0 equiv) was added to the reaction mixture.[12] After stirring for another 2 h, the desired benz[*e*]indole **4a** was obtained in 79% yield along with spiro[indene-1,3′-pyrrole] **5a** in 6% yield (Table 1, entry 1). Decreasing the amount of NaH to 2.0 equiv lead to lower yield (65%) of **4a** after prolonged reaction time (Table 1, entry 2). Addition of electrophile I_2 to the reaction mixture prior to the formation of intermediate **3a** inhibited the [3 + 2]-cycloaddition, and starting material **1a** was recovered (Table 1, entry 3). Among the screened bases such as NaH, *t*-BuOK, and NaOH (Table 1, entries 1, 4, and 5), NaH is optimal (Table 1, entry 1). Other metal catalysts such as $PtCl_2$ and $AuCl(PPh_3)$[7d,f] were also screened besides iodine (Table 1, entries 6 and 7), but they were not compatible with these strong basic reaction conditions. Different solvents were also surveyed, with toluene giving comparable yield of **4a**, but the [3 + 2]-cycloaddition reaction was slower (Table 1, entry 8 vs 1). To our delight, the regioselectivity of this tandem one-pot reaction could be controlled by solvent (Table 1, entries 9−12). The spiro-[indene-1,3′-pyrrole] **5a** became the major product when the reaction was performed in THF (Table 1, entries 12−14). Increasing the amount of I_2 to 4.0 equiv improved the yield of **5a** to 57% (Table 1, entry 14). Thus, benz[*e*]indole **4a** and spiro[indene-1,3′-pyrrole] **5a** could be selectively obtained in good to high yields by performing the reaction in different solvents (Table 1, entries 1 and 14).

With the optimal conditions in hand (Table 1, entry 1), various alkyne-tethered chalcones/cinnamates **1** were first explored to investigate the generality of this tandem one-pot reaction for the synthesis of benz[*e*]indoles **4**. The results are tabulated in Scheme 2. In general, a wide range of alkyne-tethered chalcones/cinnamates, which bear various functional groups were reacted smoothly with TosMIC **2** at ambient conditions, thus giving rise to the benz[*e*]indoles **4** in moderate to high yields. The R^1 group on cinnamates **1** such as electron-deficient aryl (**1a−c**), benzyl

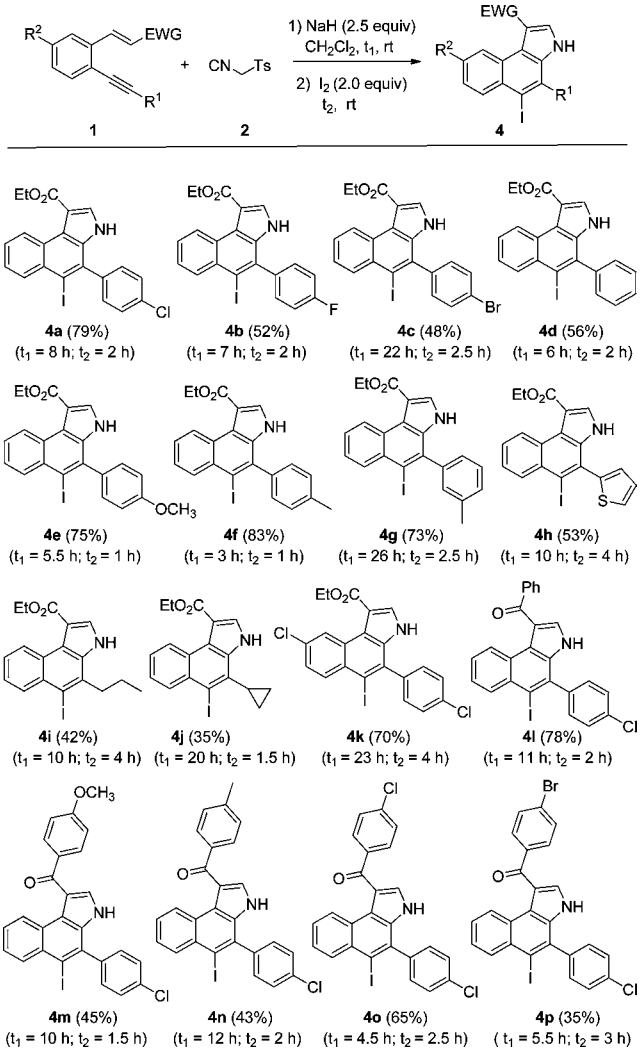
Table 1. Screening of Reaction Conditions[a]



			t (h)		yield (%)[b]	
entry	base (equiv)	solvent (equiv)	t_1	t_2	**4a**	**5a**
1	***NaH (2.5)***	***CH_2Cl_2***	***8***	***2***	***79***	***6***
2	NaH (2.0)	CH_2Cl_2	19	3	65	13
3[c]	NaH (2.5)	CH_2Cl_2	36	trace	trace	
4[d]	*t*-BuOK (2.5)	CH_2Cl_2	8	18	28	trace
5[e]	NaOH (2.5)	CH_2Cl_2	20	4	51	trace
6[f]	NaH (2.5)	CH_2Cl_2	8	21	trace	trace
7[g]	NaH (2.5)	CH_2Cl_2	8	21	trace	trace
8	NaH (2.5)	toluene	36	3	70	trace
9	NaH (2.5)	CH_3CN	0.3	16	23	40
10[h]	NaH (2.5)	DMF	0.5	24	trace	trace
11[i]	NaH (2.5)	dioxane	0.5	24	trace	12
12	NaH (2.5)	THF	0.3	12	17	42
13[j]	NaH (2.5)	THF	0.3	6.5	12	48
14[k]	***NaH (2.5)***	***THF***	***0.3***	***2.5***	***9***	***57***

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), base (0.5 mmol) and solvent (2 mL) for time 1, then I_2 (0.4 mmol) was added for time 2. [b]Isolated yields. [c]**1a**, **2**, base, and CH_2Cl_2 were added, then followed by I_2; **1a** was recovered in 70% yield. [d]**1a** was recovered in 58% yield. [e]**1a** was recovered in 28% yield. [f]$PtCl_2$ (5 mol %) instead of I_2, intermediate **3a** was obtained in 54% yield. [g]$AuCl(PPh_3)$ (1.0 mol %) and $AgSbF_6$ (4.0 mol %) instead of I_2, intermediate **3a** was obtained in 60% yield. [h]Intermediate **3a** was obtained in 45% yield. [i]Intermediate **3a** was obtained in 47% yield. [j]3.0 equiv of I_2 was used. [k]4.0 equiv of I_2 was used.

Scheme 2. Synthesis of Benz[*e*]indoles 4[a,b]



[a]Reactions were carried out with **1** (0.2 mmol), **2** (0.4 mmol), and NaH (2.5 equiv) in CH_2Cl_2 (2 mL) for time 1, then I_2 (2.0 equiv) was added for time 2 at room temperature. [b]Isolated yields.

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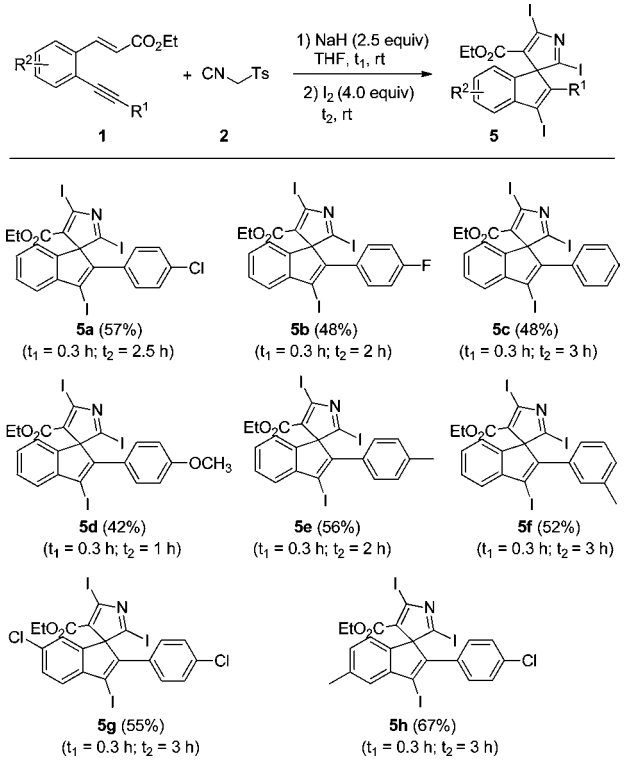
(**1d**), electron-rich aryl (**1e**–**g**), hetereoaryl (**1h**), and alkyl(**1i** and **1j**) groups were well tolerated. Cinnamate **1k** bearing a chlorine atom at R^2 also gave the corresponding benz[*e*]indole **4k** in high yield. Furthermore, alkyne-tethered chalcones **1** with both electron-donating and electron-withdrawing groups on the aryl group afforded the benz[*e*]indoles **4l**–**r** in moderate to high yields. The structure of product **4a** was further confirmed by the X-ray diffraction studies.[13]

In the transformation of cinnamate **1** to spiro[indene-1,3′-pyrrole] **5**, the elemental iodine acts as an electrophile not only to activate the triple bond but also as to iodinate the *in situ* formed pyrrole, and the 1-*H* pyrrole was dearomatized to 2-*H* pyrrole derivatives. Then, the scope of the tandem one-pot synthesis of spiro[indene-1,3′-pyrrole] **5** was also investigated with selected alkyne-tethered cinnamates **1** (Scheme 3). Cinnamates **1** bearing

Scheme 3. Synthesis of Spiro[indene-1,3′-pyrrole] 5[a,b]

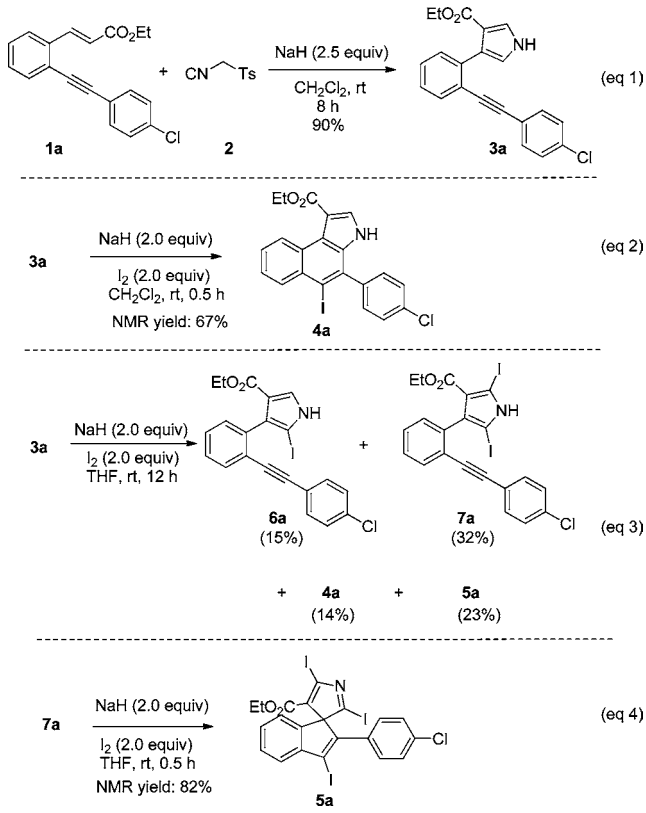


[a]Reactions were carried out with **1** (0.2 mmol), **2** (0.4 mmol), and NaH (2.5 equiv) in THF (2 mL) for time 1, then I_2 (4.0 equiv) was added for time 2 at room temperature. [b]Isolated yields.

various R^1 groups such as electro-deficient aryl, benzyl, and electro-rich aryl groups afforded the spiro[indene-1,3′-pyrroles] **5a**–**f** in good yields. Both electron-deficient and electron-rich R^2 groups on the cinnamates **1** were well tolerated, and the corresponding spiro[indene-1,3′-pyrroles] **5g** and **5h** were produced in high yields. The structure of product **5a** was further confirmed by the X-ray diffraction studies.[14]

To shed light on the reaction mechanism of this divergent tandem one-pot process, several control experiments were performed. First, when cinnamate **1a** and TosMIC **2** were treated with NaH (2.5 equiv) at room temperature in CH_2Cl_2 for 8 h, the pyrrole intermediate **3a** was isolated in 90% yield (Scheme 4, eq 1). Treatment of pyrrole **3a** with I_2 (2.0 equiv) and NaH (2.0 equiv) at room temperature in CH_2Cl_2 for 0.5 h led to formation of benz[*e*]indoles **4a** in 67% NMR yield (Scheme 4, eq 2). The

Scheme 4. Control Experiments



otherwise identical reaction in THF for 12 h afforded the diiodinated pyrrole **7a** in 32% yield along with monoiodinated pyrrole **6a**, benz[*e*]indoles **4a**, and spiro[indene-1,3′-pyrroles] **5a** in 15%, 14%, and 23% yields, respectively (Scheme 4, eq 3). Finally, when the diiodinated pyrrole **7a** was treated with I_2 (2.0 equiv) and NaH (2.0 equiv) at room temperature in THF for 0.5 h, the spiro[indene-1,3′-pyrroles] **5a** was obtained in 82% NMR yield (Scheme 4, eq 4). These results uncover the identity of **3a** and **7a** being the intermediates in the formation of benz[*e*]-indoles **4a** and spiro[indene-1,3′-pyrroles] **5a**, respectively.

On the basis of the above results and the related work,[7] a mechanistic pathway for the divergent tandem one-pot synthesis of benz[*e*]indoles **4** and spiro[indene-1,3′-pyrroles] **5** is proposed in Scheme 5 (with the transformation of **1a** with **2** as an example). First, the formal [3 + 2]-cycloaddition of cinnamate **1a** with TosMIC **2** under basic conditions provides the pyrrole intermediate **3a**, preceding the two competing pathways depicted as follows. In *path a* for the formation of benz[*e*]indole **4a**, the carbon–carbon triple bond is activated by the coordination of I_2 to form the intermediate **I** and subsequent intramolecular 6-*endo*-dig cyclization occurs by the attack of the α-position of pyrrole to the triple bond to give the fused 2-*H* pyrrole intermediate **II**. The benz[*e*]indoles **4a** is produced after deprotonation and aromatization. In *path b* for the formation of spiro[indene-1,3′-pyrrole] **5a**, an electrophilic bisiodination of pyrrole **3a** occurs with elemental iodine to furnish **7a**,[15] which underwent iodine promoted 5-*endo*-dig cyclization and deprotonation to give the spiro[indene-1,3′-pyrroles] **5a**.

In summary, we have developed a solvent-dependent divergent tandem one-pot synthesis of benz[*e*]indoles and spiro[indene-1,3′-pyrroles] from readily available alkyne-tethered chalcones/cinnamates and TosMIC. In these one-pot processes, two structurally distinct scaffolds were efficiently

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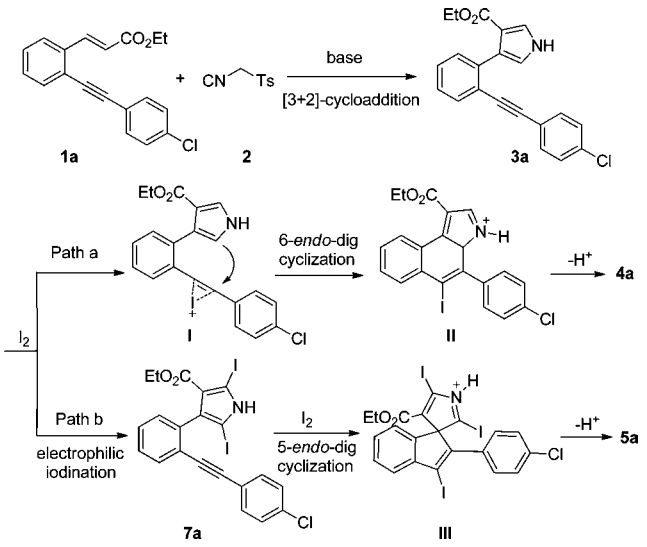
Scheme 5. Proposed Mechanism for Formation of Benz[*e*]indoles 4 and Spiro[indene-1,3′-pyrroles] 5



constructed with successive formation of four to six new bonds. This reaction features high efficiency, mild reaction conditions, broad substrate scope, and readily available substrates. Further investigations on the bicyclization strategy of activated methylene isocyanides for the divergent synthesis of complex architecture are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds and X-ray data of **4a** and **5a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01676.

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1400168 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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