

An Efficient Route to Tetrahydroindeno[2,1-*b*]pyrroles via a Base-Promoted Reaction of (*E*)-2-Alkynylphenylchalcone with 2-Isocyanoacetate

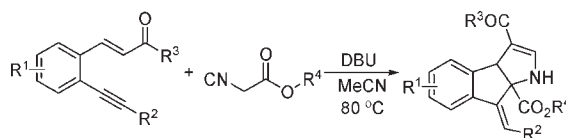
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Received October 9, 2011

ABSTRACT



A base-promoted cascade reaction of (*E*)-2-alkynylphenylchalcone with 2-isocyanoacetate provides a novel and efficient route for the synthesis of tetrahydroindeno[2,1-*b*]pyrroles. The reaction proceeds smoothly in air under mild conditions with high efficiency.

Currently, diversity-oriented synthesis has been used as an efficient strategy for the generation of natural product-like compounds to address the challenge posed by chemical genetics.¹ Thus, natural product-like compounds with privileged scaffolds which are known to be prone to display different biological activities are in great demand. Among the approaches applied for the generation of these

compounds, the cascade reaction has been demonstrated as an ideal method.^{2,3} Recently, we have constructed a small library of indene compounds with structural diversity via cascade reactions.⁴ The compounds (Figure 1) include indene-incorporated quinolines **A**,^{4a,c} chromenes **B**,^{4b} and seven-membered ring lactams **C**.^{4d} The subsequent biological assay disclosed several hits for inhibition of HCT-116. In order to find more active compounds, we need to explore efficient methods for facile assembly of other indene-incorporated heterocycles. Herein, we wish to

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report our recent efforts for the generation of indene incorporated 2,3-dihydro-1*H*-pyrroles **D** via a base-promoted reaction of (*E*)-2-alkynylphenylchalcone with 2-isocyanoacetate under mild conditions.

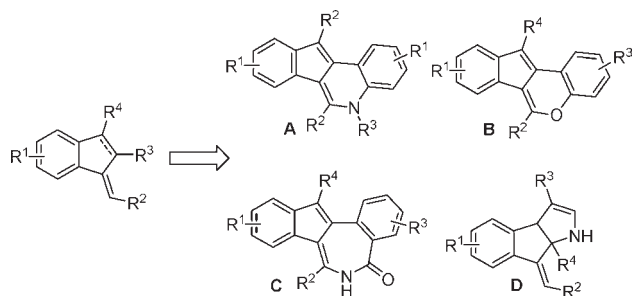
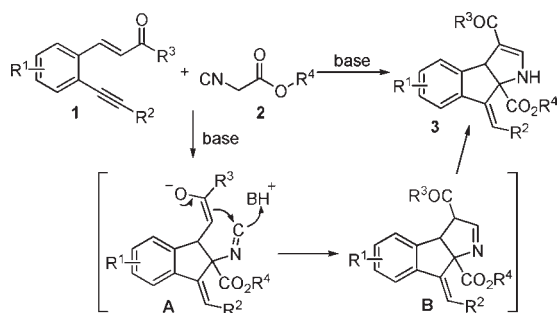


Figure 1. Indene compounds.

(*E*)-2-Alkynylphenylchalcone is a versatile synthon since there is a Michael acceptor and a triple bond in the structure. As a useful building block, 2-isocyanoacetate has been widely used in organic synthesis.^{5,6} For instance, Liu and co-workers employed 2-isocyanoacetate as a substrate for the formation of *N*-heterocycles.^{6a} Based on our recent studies on the transformation of (*E*)-2-alkynylphenylchalcones⁷ and prompted by the advancement of 2-isocyanoacetate chemistry, we conceived that tetrahydroindeno[2,1-*b*]pyrrole **3** could be prepared via a base-promoted cascade reaction of (*E*)-2-alkynylphenylchalcone with 2-isocyanoacetate. The proposed synthetic route was presented in Scheme 1. We envisioned that a nucleophilic attack of 2-isocyanoacetate **2** to (*E*)-2-alkynylphenylchalcone **1** would occur first in the presence of a base. Then isocyanide would be involved in the intramolecular reaction of enolate **A**, which would afford the compound **B**. The subsequent 1,3-*H* shift took place to furnish the expected compound **3**. To validate the feasibility of this hypothesis, we started to explore the possibility of this conversion.

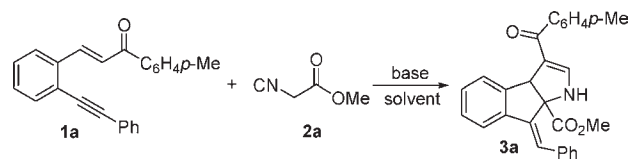
Scheme 1. Proposed Synthetic Route for the Generation of Tetrahydroindeno[2,1-*b*]pyrrole **3** via a Base-Promoted Cascade Reaction of (*E*)-2-Alkynylphenylchalcone **1** with 2-Isocyanoacetate **2**



Initially, (*E*)-2-alkynylphenylchalcone **1a** and methyl 2-isocyanoacetate **2a** were selected as the model substrates

(Table 1). The reaction was performed in the presence of 1.0 equiv of Na₂CO₃ in MeCN at 80 °C (Table 1, entry 1). To our delight, the expected tetrahydroindeno[2,1-*b*]pyrrole **3a** was isolated in 58% yield. The structure of product **3a** was unambiguously demonstrated by X-ray diffraction analysis (see the Supporting Information). Furthermore, the reaction could occur under an air atmosphere without loss of yield and efficiency. These results encouraged us for further exploration. We next screened other bases, such as NaOH, Et₃N, *t*-BuOK, and DBU (Table 1, entries 2–5). Gratifyingly, the reaction worked efficiently when DBU was employed as the base, which gave rise to the desired product in 85% yield. No better results were obtained when different solvents were subsequently screened (Table 1, entries 6–11). The yield was reduced when the reaction took place at a lower temperature (data not shown in Table 1).

Table 1. Initial Studies for the Base-Promoted Cascade Reaction of (*E*)-2-Alkynylphenylchalcone **1a** with 2-Isocyanoacetate **2a**



entry	base	solvent	yield (%) ^a
1	Na ₂ CO ₃	MeCN	58
2	NaOH	MeCN	55
3	Et ₃ N	MeCN	21
4	<i>t</i> -BuOK	MeCN	47
5	DBU	MeCN	85
6	DBU	1,4-dioxane	45
7	DBU	DCE	29
8	DBU	toluene	30
9	DBU	DMSO	39
10	DBU	DMF	56
11	DBU	EtOH	complex

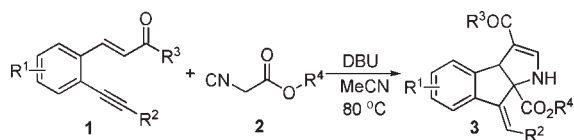
^a Isolated yield based on (*E*)-2-alkynylphenylchalcone **1a**.

The scope of this base-promoted cascade reaction of (*E*)-2-alkynylphenylchalcone **1** with 2-isocyanoacetate **2** was then investigated under the optimized conditions (1.0 equiv of DBU, MeCN, 80 °C). The results are presented in Table 2. In most cases, (*E*)-2-alkynylphenylchalcone **1** reacted with methyl 2-isocyanoacetate **2a** leading to the desired products in good yields. For the R³ group in the substrate (*E*)-2-alkynylphenylchalcone **1**, not only aryl

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Table 2. Scope Investigation for the Base-Promoted Cascade Reaction of (*E*)-2-Alkynylphenylchalcone **1** with 2-Isocyanoacetate **2**

entry	R ¹ , R ² , R ³	R ⁴	product	yield (%) ^a	entry	R ¹ , R ² , R ³	R ⁴	product	yield (%) ^a
1	H, Ph, 4-MeC ₆ H ₄ (1a)	Me (2a)		85 (3a)	8	4,5-(OMe) ₂ , Ph, 4-MeC ₆ H ₄ (1h)	Me (2a)		77 (3h)
2	H, Ph, 4-MeOC ₆ H ₄ (1b)	Me (2a)		44 (3b)	9	5-F, Ph, 4-MeC ₆ H ₄ (1i)	Me (2a)		78 (3i)
3	H, Ph, Ph (1c)	Me (2a)		76 (3c)	10	H, 4-MeC ₆ H ₄ , 4-MeC ₆ H ₄ (1j)	Me (2a)		58 (3j)
4	H, Ph, 4-ClC ₆ H ₄ (1d)	Me (2a)		56 (3d)	11	H, 4-MeOC ₆ H ₄ , 4-MeC ₆ H ₄ (1k)	Me (2a)		51 (3k)
5	H, Ph, 4-BrC ₆ H ₄ (1e)	Me (2a)		57 (3e)	12	H, H, 4-MeOC ₆ H ₄ (1l)	Me (2a)		60 (3l)
6	H, Ph, ⁿ Pr (1f)	Me (2a)		61 (3f)	13	H, ⁿ Bu, Ph (1m)	Me (2a)	-	complex
7	5-Me, Ph, 4-MeC ₆ H ₄ (1g)	Me (2a)		74 (3g)	14	H, Ph, 4-MeC ₆ H ₄ (1a)	^t Bu (2b)		80 (3m)
					15	4,5-(OMe) ₂ , Ph, 4-MeC ₆ H ₄ (1h)	^t Bu (2b)		68 (3n)
					16	5-F, Ph, 4-MeC ₆ H ₄ (1i)	^t Bu (2b)		80 (3o)

^a Isolated yield based on (*E*)-2-alkynylphenylchalcone **1**.

groups but also alkyl groups are all tolerated in the reaction of methyl 2-isocyanoacetate **2a**. For instance, reaction of methyl 2-isocyanoacetate **2a** and compound **1c** with a phenyl group attached on the position of R³ gave rise to the corresponding product **3c** in 76% yield (Table 2, entry 3). While the R³ position was changed to an *n*-propyl group, the expected product **3f** was afforded in 61% yield (Table 2, entry 6). Reactions of methyl 2-isocyanoacetate **2a** and (*E*)-2-alkynylphenylchalcones **1** with different substitutions on the aromatic ring were then studied (Table 2, entries 7–9). As expected, all reactions proceeded smoothly to furnish the desired products in good yields. Next, reactions of (*E*)-2-alkynylphenylchalcones **1**

with various substitutions on the R² position were examined (Table 2, entries 10–13). It was noteworthy that the terminal alkyne in (*E*)-2-alkynylphenylchalcone **1l** could be tolerated under the standard conditions (Table 2, entry 12). Additionally, this reaction seemed to be sensitive for the (*E*)-2-alkynylphenylchalcone **1** with an alkyl group attached to the triple bond. The result was complex when (*E*)-2-alkynylphenylchalcone **1m** was employed in the

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reaction of methyl 2-isocyanoacetate **2a** (Table 2, entry 13). Further investigation revealed that *tert*-butyl 2-isocyanoacetate **2b** was a suitable reactant as well, and the corresponding products were generated in good yields (Table 2, entries 14–16). All products were uniformly formed as the *Z*-isomer. This might be due to a kinetic result according to Baldwin's rules.⁸

In conclusion, we have described a novel and efficient route for the construction of tetrahydroindeno[2,1-*b*]pyrroles via a base-promoted cascade reaction of (*E*)-2-alkynylphenylchalcone with 2-isocyanoacetate. The reaction could be performed in air under mild conditions

without loss of efficiency. Efforts for its library generation using solution parallel synthesis are currently ongoing.

Acknowledgment. Financial support from National Natural Science Foundation of China (Nos. 21032007 and 21172038) is gratefully acknowledged.

Supporting Information Available. Experimental procedure, characterization data, ¹H and ¹³C NMR spectra of compounds **3**, and a CIF file of compound **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.