ORGANIC LETTERS

2012
Vol. 14, No. 11
2655–2657

An Unexpected Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldehyde with 2-Isocyanoacetate

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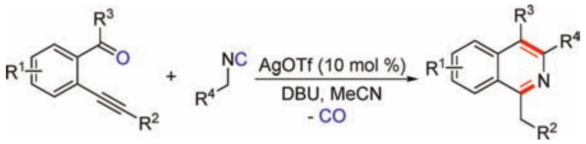
Received April 8, 2012

ABSTRACT



An unexpected silver triflate catalyzed reaction of 2-alkynylbenzaldehyde with 2-isocyanoacetate provides an efficient route for the generation of isoquinolines. The reaction proceeds smoothly in air under mild conditions with high efficiency.

In the past decade, we have witnessed significant progress in the pursuit of efficient methods for the preparation of natural product-like compounds with privileged scaffolds in the studies of chemical genetics.[1] We have also been involved in the construction of small libraries of *N*-heterocycles using the strategy of diversity-oriented synthesis.[2] Recently, we reported an efficient route for the synthesis of tetrahydroindeno[2,1-*b*]pyrroles via a base-promoted tandem reaction[3] of (*E*)-2-alkynylphenylchalcone with 2-isocyanoacetate (Scheme 1, eq 1).[2a] From this result, we recognized that 2-isocyanoacetate, which has been widely used in organic synthesis,[4,5] was a useful building block for the generation of *N*-heterocycles. Since (*E*)-2-alkynylphenylchalcone is prepared from a condensation of 2-alkynylbenzaldehyde with an active methylene compound, we envisioned that 2-alkynylbenzaldehyde might be applied in the reaction with isocyanoacetate as well due to their structural similarity. The proposed transformation is presented in Scheme 1. We anticipated that an oxazole-incorporated compound **C** would be formed via a similar process (Scheme 1, eq 2). We began our studies with the

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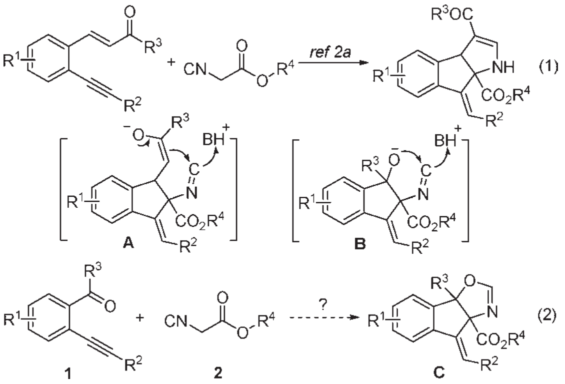
10.1021/ol300901x

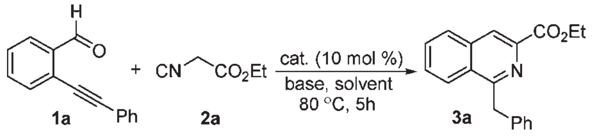
reaction of 2-alkynylbenzaldehyde **1a** with isocyanoacetate **2a**. Initially, the reaction was performed in the presence of DBU (1.0 equiv) in MeCN at 80 °C (Table 1, entry 1). To our surprise, isoqunioline **3a** was obtained instead of compound **C** with a 62% isolated yield.

Scheme 1. A Proposed Reaction of 2-Alkynylbenzaldehyde with Isocyanoacetate



It is well-known that isoquinoline is a ubiquitous core in many natural products and small molecule chemotherapeutics, which possess diverse pharmacological properties.[6] So far, a remarkable advance has been made in the synthesis of isoquinolines.[7–9] For instance, isoquinoline derivatives could be generated via a metal-catalyzed cyclization of *ortho*-alkynylaryl aldimines.[8] Pyrrolo-isoquinolines related to the Lamellarins could be prepared using a silver-catalyzed tandem cycloisomerization/dipolar cycloaddition.[9a] However, efficient catalytic methods for the generation of diverse isoquinolines are still in great demand. This unexpected result would provide an alternative route for these molecules. Additionally, we believe this protocol would represent a significant advance in the area of isoquinoline chemistry. With the above interesting result in hand, we started to explore the optimal conditions (Table 1). Different bases were examined (Table 1, entries 2–7). However, no improvement was observed. We further explored the reaction in various solvents, and acetonitrile was demonstrated as the best choice (Table 1, entries 8–14). A similar outcome (65% yield) was obtained when the reaction was performed at 110 °C (Table 1, entry 15). The yield was lower when the reaction temperature was reduced. Since the process was related to a cyclization of the triple bond, metal salts were then screened (Table 1, entries 16–24). Gratifyingly, the reaction worked efficiently when silver triflate was added, which afforded the corresponding product **3a** in 90% yield.

Table 1. Initial Studies for the Reaction of 2-Alkynylbenzaldehyde **1a** with 2-Isocyanoacetate **2a**



entry	cat.	base	solvent	yield (%)[a]
1	–	DBU	MeCN	62
2	–	NaOH	MeCN	24
3	–	Cs_2CO_3	MeCN	31
4	–	Et_3N	MeCN	N.D.
5	–	K_3PO_4	MeCN	58
6	–	$NaOCH_3$	MeCN	30
7	–	*t*-BuOK	MeCN	42
8	–	DBU	DMF	trace
9	–	DBU	DMSO	25
10	–	DBU	toluene	30
11	–	DBU	1,4-dioxane	N.D.
12	–	DBU	THF	20
13	–	DBU	DCE	N.D.
14	–	DBU	EtOH	27
15[b]	–	DBU	MeCN	65
16	AgOTf	DBU	MeCN	90
17	$Cu(OTf)_2$	DBU	MeCN	58
18	$FeCl_3$	DBU	MeCN	58
19	$CuCl_2$	DBU	MeCN	30
20	$Bi(OTf)_3$	DBU	MeCN	35
21	CuI	DBU	MeCN	65
22	$PdCl_2$	DBU	MeCN	73
23	$Pd(OAc)_2$	DBU	MeCN	44
24	AuCl	DBU	MeCN	63

[a] Isolated yield based on 2-alkynylbenzaldehyde **1a**. [b] The reaction occurred at 110 °C.

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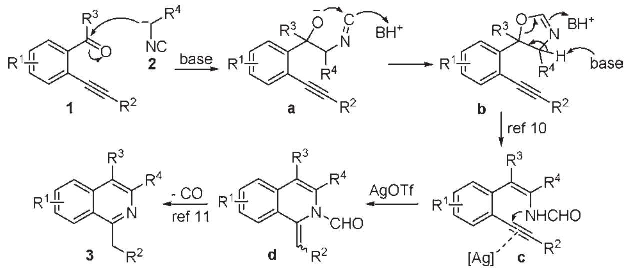
A possible mechanism is presented in Scheme 2. We hypothesized that isocyanoacetate **2** would attack 2-alkynylbenzaldehyde **1** first in the presence of a base to generate an intermediate **a**. Then isocyanide would be involved to afford oxazole **b**, which would undergo a rearrangement to furnish compound **c**.[10] The subsequent 6-*exo* cyclization would occur in the presence of silver triflate to generate the isoquinoline **3** with a loss of carbon monoxide.[11]

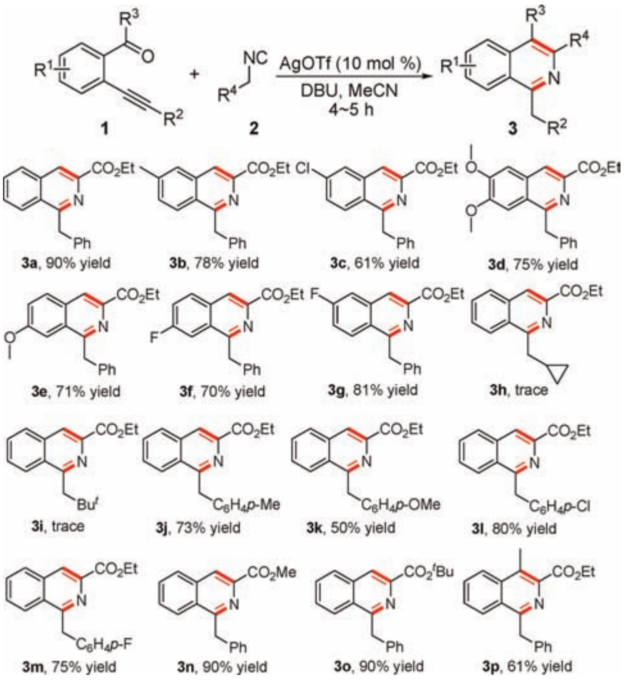
Scheme 2. A Proposed Mechanism for the Generation of Isoquinioline **3** via a Reaction of 2-Alkynylbenzaldehyde **1** with 2-Isocyanoacetate **2**



We next explored the scope of this cascade reaction of 2-alkynylbenzaldehyde **1** with 2-isocyanoacetate **2** under the optimized conditions (1.0 equiv of DBU, 10 mol % of AgOTf, MeCN, 80 °C). The results are summarized in Scheme 3. We found that the substituents on the aromatic ring of 2-alkynylbenzaldehyde **1** did not hamper the reaction process. Reactions of methyl-, methoxy-, chloro-, or fluoro-substituted 2-alkynylbenzaldehyde **1** with 2-isocyanoacetates **2** all worked well to afford the desired products in good yields. However, the group attached on the triple bond of 2-alkynylbenzaldehyde **1** was crucial for the successful transformation. It was found that the reactions were suitable for the 2-alkynylbenzaldehydes **1** with an aryl group attached to the triple bond. The reactions failed when 2-alkynylbenzaldehydes **1** with an alkyl group attached to the triple bond were employed. Methyl and *tert*-butyl 2-isocyanoacetates were examined in the meantime. As expected, the reactions proceeded smoothly to give the corresponding products in good yields. The structure of isoquinoline **3n** was unambiguously illustrated by X-ray diffraction analysis (see the Supporting Information). Additionally, a ketone was a suitable substrate as well in the reaction of ethyl 2-isocyanoacetate under the standard conditions, which gave rise to product **3p** in 61% yield.

In conclusion, we have described an efficient silver triflate catalyzed reaction of 2-alkynylbenzaldehyde with 2-isocyanoacetate. The reaction occurs in air under mild conditions without loss of efficiency, leading to isoquinolines in good yields. Use of 2-isocyanoacetates for the generation other *N*-heterocycles is ongoing in our laboratory.

Scheme 3. Scope Investigation for the Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldehyde **1** with 2-Isocyanoacetate **2**



[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

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

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

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The authors declare no competing financial interest.