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Highly efficient electrophilic cyclization of *N*′-(2-alkynylbenzylidene)hydrazides

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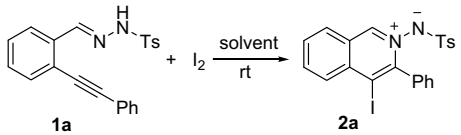
ABSTRACT

Electrophilic cyclization of *N*′-(2-alkynylbenzylidene)hydrazides with I_2, Br_2, or ICl under mild conditions is described. This reaction proceeds smoothly in dichloromethane at room temperature, which provides a useful method for the synthesis of functionalized isoquinolinium-2-yl amide.

In pursuit of identifying small molecule ligands for studying biological function as well as potential candidates as a lead compound,[1] we have explored efficient methodologies for the synthesis of natural product-like molecules.[2] Since the isoquinoline skeleton is an important substructure in both natural products and therapeutic agents, as well as the wide application of isoquinolines in pharmaceutical research,[3] the development of efficient methods for isoquinoline and related derivatives synthesis has continuously attracted the attentions of many chemists. Recently, we have developed efficient methods for synthesis of diverse 1,2-dihydroisoquinolines via multi-component tandem reactions starting from 2-alkynylbenzaldehyde or 2-alkynylbenzaldoxime.[2] With a hope of finding more active hits or leads for our particular biological assays, it is still highly desired to construct the new isoquinoline-based structures. Herein, we present our recent efforts for the synthesis of functionalized isoquinolinium-2-yl amide via electrophilic cyclization of *N*′-(2-alkynylbenzylidene)hydrazides with I_2, Br_2, or ICl under mild conditions.

The electrophilic cyclization of heteroatomic nucleophiles such as oxygen, nitrogen, sulfur, and phosphorus with tethered alkynes has proven to be an effective method for preparing a large variety of heterocyclic ring systems.[4,5] The electrophiles such as iodine, bromine, and ICl were commonly used in the reaction since the resulting iodine- or bromo-containing products are readily elaborated to more complex products by using known organopalladium chemistry. Recently, we and others discovered that in the presence of electrophiles (such as iodine or bromine) or Lewis acid, 2-alkynylbenzaldoxime would be transferred to isoquinoline-*N*-oxide via electrophilic cyclization.[6] Prompted by the results, we envisioned that *N*′-(2-alkynylbenzylidene)hydrazide might be utilized as starting material for synthesis of new isoquinoline-based compounds due to the structural similarity with 2-alkynylbenzaldoxime. We reasoned that in the presence of electrophiles such as iodine or bromine, *N*′-(2-alkynylbenzylidene)hydrazide would undergo electrophilic cyclization, leading to isoquinolinium-2-yl amides. Thus, we started to investigate the possibility of this electrophilic cyclization reaction of *N*′-(2-alkynylbenzylidene)-hydrazide.

The reaction was initially studied with *N*′-(2-alkynylbenzylidene)hydrazide **1a** and iodine, which were selected as model substrates (Scheme 1). As expected, the reaction proceeded smoothly



DCM	99%	THF	82%
DCE	94%	MeCN	97%
Et_2O	88%	$MeNO_2$	98%
toluene	96%		

Scheme 1.

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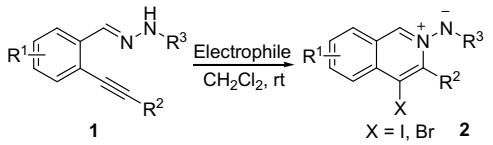
Table 1
Electrophilic cyclization reaction of *N*′-(2-alkynylbenzylidene)hydrazides[a,7]



Electrophile: I_2, ICl, or Br_2

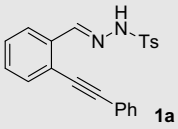
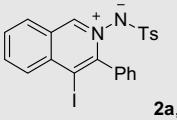
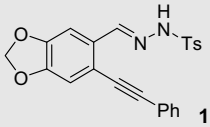
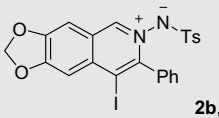
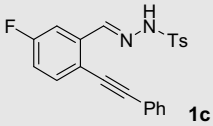
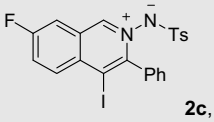
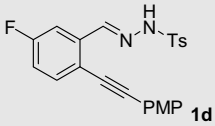
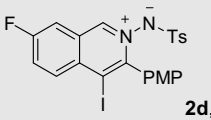
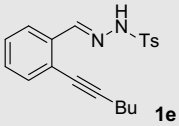
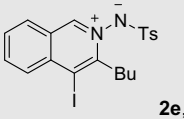
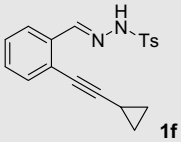
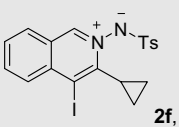
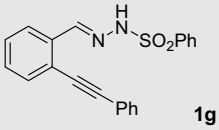
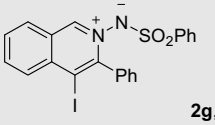
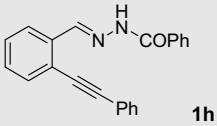
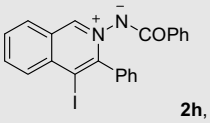
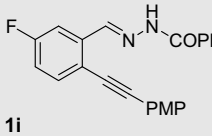
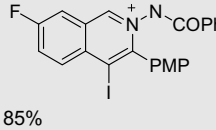
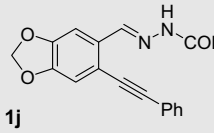
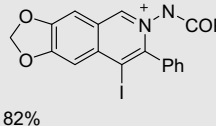
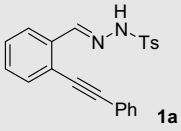
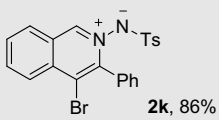
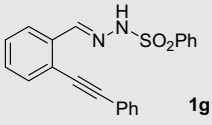
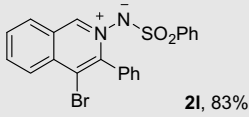
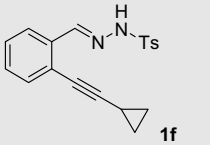
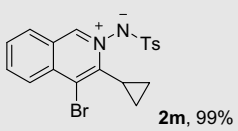
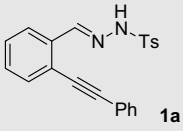
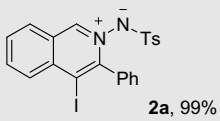
Entry	Substrate	E	Product
1	 **1a**	I_2	 **2a**, 99%
2	 **1b**	I_2	 **2b**, 93%
3	 **1c**	I_2	 **2c**, 86%
4	 **1d**	I_2	 **2d**, 99%
5	 **1e**	I_2	 **2e**, 94%
6	 **1f**	I_2	 **2f**, 92%
7	 **1g**	I_2	 **2g**, 84%
8	 **1h**	I_2	 **2h**, 70%
9	 **1i**	I_2	 **2i**, 85%
10	 **1j**	I_2	 **2j**, 82%

Table 1 (*continued*)

Entry	Substrate	E	Product
11	 **1a**	Br_2	 **2k**, 86%
12	 **1g**	Br_2	 **2l**, 83%
13	 **1f**	Br_2	 **2m**, 99%
14	 **1a**	ICl	 **2a**, 99%

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

in dichloromethane at room temperature to afford the desired product **2a** in 99% yield. Similar results were observed when other solvents were screened. From these results, it was found that this reaction was highly efficient under extremely mild conditions.

With this preliminary optimized conditions in hand, the scope of this reaction was then investigated (CH_2Cl_2, rt), and the results are summarized in Table 1. We rapidly noticed the broad field of application of the process and its remarkable functional group compatibility. For all cases, *N*′-(2-alkynylbenzylidene)hydrazide **1** reacted with various electrophiles leading to the corresponding products **2** in good to excellent yields. Usually, only 5 min to 2 h was needed for completion of reaction. For instance, reaction of *N*′-(2-alkynylbenzylidene)hydrazide 1**b** with iodine under the standard conditions gave rise to the desired product **2b** in 93% yield (Table 1, entry 2). An 86% yield was obtained when fluoro-substituted *N*′-(2-alkynylbenzylidene)-hydrazide **1c** was utilized as substrate (Table 1, entry 3). No difference was observed when the group attached on the triple bond was changed. For example, reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1d** and iodine afforded the corresponding isoquinolinium-2-yl amide **2d** in almost quantitative yield (Table 1, entry 4, 99% yield). When the aryl group attached on the triple bond was replaced by *n*-butyl or cyclopropyl group, similar yield was isolated (Table 1, entries 5 and 6). The reactions also worked well when tosyl group on the nitrogen in *N*′-(2-alkynylbenzylidene)hydrazide **1** was changed to other groups, such as benzoyl group (Table 1, entries 8–10). Reactions of *N*′-(2-alkynylbenzylidene)hydrazides **1** with other electrophiles were also examined. For example, 86% yield of product **2k** was generated when *N*′-(2-alkynylbenzylidene)hydrazide **1a** was employed in the reaction of bromine (Table 1, entry 11), while 83% yield of product **2l** was isolated when substrate **1g** was used under the conditions shown in (Table 1, entry 12). Reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1f** or **1a** with bromine or ICl also proceeded well to give rise to the corresponding products in quantitative yields (Table 1, entries 13 and 14).

In summary, we have described a highly efficient electrophilic cyclization of *N*′-(2-alkynylbenzylidene)-hydrazide with I_2, Br_2, or ICl in dichloromethane at room temperature. This reaction proceeds smoothly under extremely mild conditions, which provides

a useful method for the synthesis of functionalized isoquinolinium-2-yl amides. Further transformation of the products is under investigation in our laboratory, and the results will be reported in due course.

Acknowledgments

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7. *General procedure for electrophilic cyclization reaction of N′-(2-alkynylbenzylidene)hydrazides*: An electrophile (2.0 equiv of I_2 or 1.0 equiv of Br_2, ICl) in 2.0 mL of CH_2Cl_2 was added dropwise to a mixture of *N′*-(2-alkynylbenzylidene)hydrazide **1** (0.30 mmol) in CH2Cl2 (4.0 mL). The reaction mixture was stirred at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was then diluted with CH_2Cl_2 (25 mL), washed with saturated aqueous $Na_2S_2O_3$ (25 mL), dried (Na_2SO_4) and filtered. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **2**.