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Lewis acid-catalyzed reactions of *N*′-(2-alkynylbenzylidene)hydrazides with diethyl phosphite

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ABSTRACT

Lewis acid catalyst-tuned reactions of *N*′-(2-alkynylbenzylidene)hydrazides with diethyl phosphite are described. Isoquinolin-1-ylphosphonate is generated when copper triflate is utilized as catalyst, while 2-amino-1,2-dihydroisoquinolin-1-ylphosphonate is obtained in the presence of palladium acetate.

Isoquinolines, including 1,2-dihydroisoquinolines are common structural motifs in many natural products and pharmaceuticals that exhibit remarkable biological activities.[1] Thus, many efforts have been given for the development of new methods for their constructions.[2–4] Recently, we have focused on the methodology development for the expeditious synthesis of biologically relevant heterocyclic compounds.[4,5] For example, 1,2-dihydroisoquinolines could be generated via three-component tandem reactions[6,7] of 2-alkynylbenzaldehyde, amine, and various nucleophiles.[4] Screening in a PTP1B (protein tyrosine phosphatase) inhibition assay led to the identification of a hit with a promising IC_{50} value of 4.6 μM. The discovery of promising lead compounds and their moderate activity warranted the development of efficient and rapid syntheses and evaluations of analogous structures in the search for better inhibitors. Thus, subsequently the related heterocycles were synthesized via tandem reactions starting from 2-alkynylbenzaldoxime **A** or 2-(2-(alkynyl)benzylidene)malonate **B**.[5a,b] Meanwhile, the structurally similar *N*′-(2-alkynylbenzylidene)hydrazides **C** were utilized as substrates as well to investigate the possibility for reactions with nucleophiles (Fig. 1). Herein, we disclosed our recent efforts for Lewis acid-catalyzed reactions of *N*′-(2-alkynylbenzylidene)hydrazides with diethyl phosphite, which led to different outcomes under different conditions: isoquinolin-1-ylphosphonate was generated when copper triflate was utilized as catalyst, while 2-amino-1,2-dihydroisoquinolin-1-ylphosphonate was obtained when the reaction was catalyzed by palladium acetate.

Recently, it was reported that in the presence of Lewis acid or electrophiles, isoquinoline-*N*-oxide could be formed starting from 2-alkynylbenzaldoxime **A**.[5a,5c,8] Prompted by these results, we envisaged that *N*′-(2-alkynylbenzylidene)hydrazide might undergo similar transformation catalyzed by suitable Lewis acid. It is well-known that Lewis acid-catalyzed cyclization of alkynes possessing a nucleophile in proximity to the triple bond is an important process in organic synthesis, which can construct various heterocycles efficiently.[9,10] We conceived that for reaction of *N*′-(2-alkynylbenzylidene)hydrazide with nucleophile, in the presence of Lewis acid the intermediate isoquinolinium would be generated,[11] which then underwent nucleophilic attack to give rise to the corresponding 2-amino-1,2-dihydroisoquinolines. Thus, initial studies were performed by using *N*′-(2-alkynylbenzylidene)hydrazide **1a** and diethyl phosphite **2** as model substrates, catalyzed by various Lewis acids (Scheme 1).

Firstly, the reaction was carried out in the presence of 10 mol % of Lewis acid in dichloroethane at room temperature. For most catalysts employed [such as $Zn(OTf)_2$, $Yb(OTf)_3$, $Dy(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, and AgOTf], no desired product was isolated and only

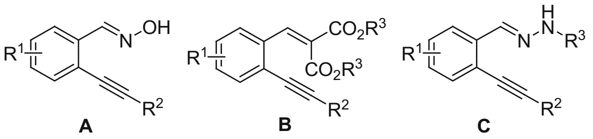

Figure 1. Structures of 2-alkynylbenzaldoxime **A**, 2-(2-(alkynyl)benzylidene)malonate **B**, and *N*′-(2-alkynylbenzylidene)hydrazide **C**.

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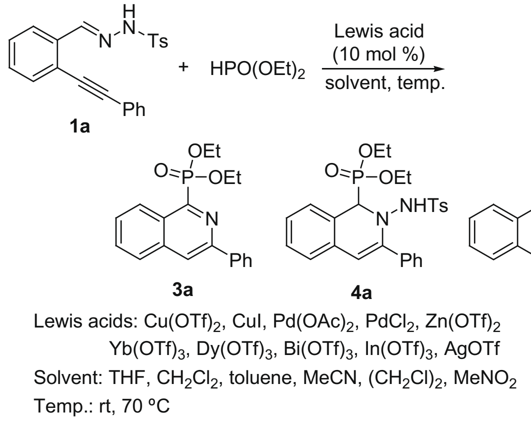


Scheme 1. Reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and diethyl phosphite **2** catalyzed by various Lewis acids.

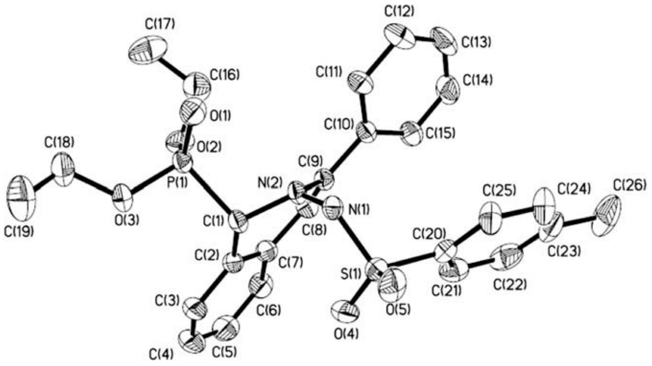
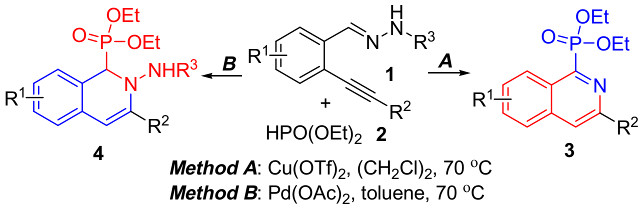


Figure 2. ORTEP diagram of 2-amino-1,2-dihydroiso-quinoline **4a**.

intermediate isoquinolinium **5a** was generated. Elevating the reaction temperature to 70 °C could not improve the result. Gratifyingly, in the presence of Pd(OAc)$_2$ (10 mol %), this reaction proceeded smoothly in dichloroethane at 70 °C to afford the desired 2-amino-1,2-dihydroisoquinoline **4a** in 45% yield. Further solvent screening revealed that the yield could be increased to 62% when toluene was utilized as a replacement. The structure of **4a** was verified by ^{1}H and ^{13}C NMR, mass spectroscopy, as well as X-ray diffraction analysis (Fig. 2, also see Supplementary data).

Table 1

Copper triflate- or palladium acetate-catalyzed reactions of *N*′-(2-alkynylbenzylidene)hydrazides **1** with diethyl phosphite **2**[a]



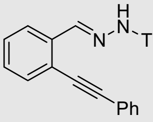
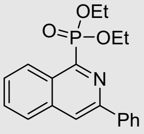
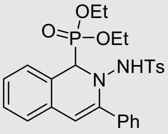
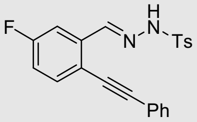
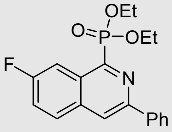
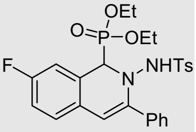
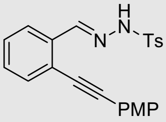
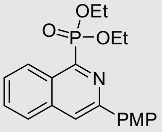
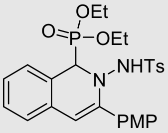
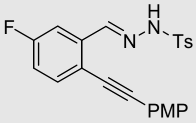
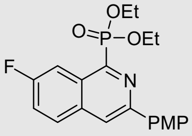
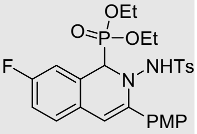
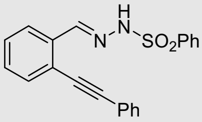
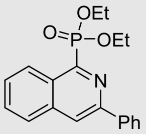
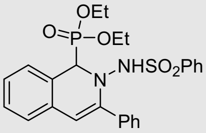
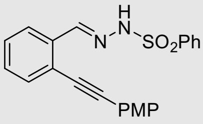
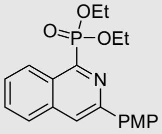
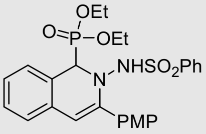
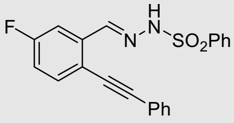
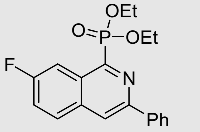
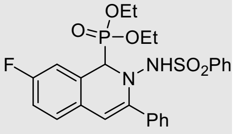
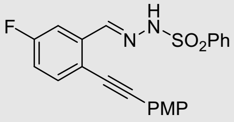
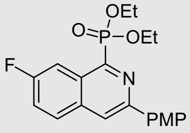
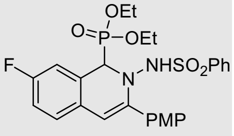
Entry	Compound **1**	Product **3**	Product **4**
1	 **1a**	 Method A: **3a**, 71%	 Method B: **4a**, 62%
2	 **1b**	 Method A: **3b**, 54%	 Method B: **4b**, 53%
3	 **1c**	 Method A: **3c**, 74%	 Method B: **4c**, 55%
4	 **1d**	 Method A: **3d**, 50%	 Method B: **4d**, 50%

Table 1 (*continued*)

Entry	Compound **1**	Product **3**	Product **4**
5	 **1e**	 Method A: **3a**, 72%	 Method B: **4e**, 60%
6	 **1f**	 Method A: **3c**, 67%	 Method B: **4f**, 57%
7	 **1g**	 Method A: **3b**, 72%	 Method B: **4g**, 70%
8	 **1h**	 Method A: **3d**, 75%	 Method B: **4h**, 64%

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

Interestingly, a different product **3a** with 71% yield was obtained when copper triflate was employed as a catalyst (DCE, 70 °C). Under this condition, other solvents displayed inferior results. This result is reasonable since in the presence of copper catalyst the amino group attached on the nitrogen of 2-amino-1,2-dihydroisoquinoline **4a** is easily released. To test this idea, reaction of 2-amino-1,2-dihydro-isoquinoline **4a** in dichloroethane at 70 °C catalyzed by copper triflate was performed. As expected, isoquinolin-1-ylphosphonate **3a** was generated. We also examined other nucleophiles (such as phenyl acetylene, methanol, and diethyl malonate) in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a**. However, no nucleophilic addition adducts were detected and only intermediate **5a** was isolated.

With this preliminary result in hand, we started to investigate the scope of these metal-tuned reactions of *N*′-(2-alkynylbenzylidene)hydrazides under palladium acetate- or copper triflate-catalyzed conditions [$Pd(OAc)_2$ (10 mol %), toluene, 70 °C; $Cu(OTf)_2$, DCE, 70 °C], and the results are shown in Table 1. The *N*′-(2-alkynylbenzylidene)hydrazides could be easily synthesized via condensation of 2-alkynylbenzaldehyde with hydrazine.[12] From Table 1, it was found that for all cases, this metal-tuned reactions of *N*′-(2-alkynylbenzylidene)hydrazides with diethyl phosphite furnished the corresponding isoquinolin-1-ylphosphonate **3** or 2-amino-1,2-dihydroisoquinoline **4** in good yields. For example, reaction of fluoro-substituted *N*′-(2-alkynylbenzylidene)hydrazide **1b** with diethyl phosphite catalyzed by copper triflate gave rise to the desired product **3b** in 54% yield, while 53% yield of product **4b** was generated when $Pd(OAc)_2$ was used as catalyst (Table 1, entry 2). When the phenyl group attached on the triple bond in *N*′-(2-alkynylbenzylidene)hydrazide **1** was replaced by 4-methoxyphenyl group, the similar yields were observed (Table 1, entry 3). However, the reaction was complicated and no desired products were generated when the phenyl group was changed to aliphatic groups (such as butyl and cyclopropyl group, data not shown in Table 1). Compound **1e** was also suitable substrate in this process, which reacted with diethyl phosphite **2** under the copper- or palladium-catalyzed conditions leading to the corresponding product **3a** or **4e** in 72% and 60% yield, respectively (Table 1, entry 5). Reactions of other substrates **1f–h** with phosphite also proceeded smoothly, which gave rise to the desired product in good yield (Table 1, entries 6–8).

In conclusion, we have described copper triflate- or palladium acetate-catalyzed reactions of *N*′-(2-alkynylbenzylidene)hydrazides with diethyl phosphite, thus offering an unprecedented and straightforward route for the synthesis of isoquinolin-1-ylphosphonate or 2-amino-1,2-dihydroisoquinolin-1-ylphosphonate. Application of *N*′-(2-alkynylbenzylidene)hydrazides in other transformations is under investigation in our laboratory, and the results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.013.

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