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Facile Synthesis of 1-(Isoquinolin-1-yl)ureas by Silver Triflate Catalyzed Tandem Reactions of 2-Alkynylbenzaldoximes with Carbodiimides

Shengqing Ye,^[a] Huanhuan Wang,^[a] and Jie Wu^{*[a,b]}

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2-Alkynylbenzaldoximes react with carbodiimides under mild conditions and silver triflate catalysis in DMF, leading to a diverse range of 1-(isoquinolin-1-yl)ureas in good to excellent yields. This transformation involves tandem 6-endo cyclization, [3+2] cycloaddition, and subsequent rearrangement.

Introduction

It is well recognized that natural product like compounds can be used to dissect the circuitry of cells in a way that is analogous to the use of mutations in genetics.^[1] One of the most efficient ways to generate such small molecules capable of modulating any pathway or process of interest is using diversity-oriented synthesis.^[2] Among the strategies using diversity-oriented synthesis to produce a collection of structurally complex and diverse compounds, tandem reactions using simple starting materials provide an efficient and powerful tool.^[3,4] As a privileged skeleton, the isoquinoline core structure is found in a wide variety of biologically active natural products and pharmaceuticals.^[5] In addition, isoquinoline derivatives with iridium complexes are found applications in organic light-emitting diodes.^[6] Thus, intense interest has been directed toward the development of new methods for the isoquinoline construction.[7-10] Although there are several routes to isoquinolines, it is still of high demand to develop novel and efficient pathways for efficient assembly of functionalized isoquinolines with novel structures under mild conditions, especially in a combinatorial format.

Recently, 2-alkynylbenzaldoxime was discovered as a useful building block for the formation of nitrogen-containing heterocycles.^[11] For example, we reported the generation of an isoquinoline-based azomethine ylide through a cascade reaction of 2-alkynylbenzaldoxime and DMAD with bromide or iodine.^[11g] Subsequently, 2-alkynylbenzaldoxime was also found to be a suitable partner in the reaction of

E-mail: jie_wu@fudan.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China
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isocyanide co-catalyzed by silver triflate and bismuth triflate, which afforded N-(isoquinolin-1-yl)formamides in good vields.^[11f] Meanwhile, Shin and co-workers disclosed the gold-catalyzed cascade reactions of 2-alkynylbenzaldoximes.^[11a] In the above reaction processes, isoquinoline Noxide was believed to be the key intermediate, which was generated from 2-alkynylbenzaldoxime through 6-endo cyclization in the presence of suitable Lewis acids or electrophiles.^[11] Prompted by these results and with an expectation to generate a focused library of isoquinolines, we conceived that carbodiimides 2 should also be suitable substrates in the reaction of 2-alkynylbenzaldoximes 1. As described in Scheme 1, we expected that [3+2] cycloaddition reaction would occur after generation of isoquinoline N-oxides 3 through 6-endo cyclization of 2-alkynylbenzaldoximes 1 in the presence of a metal catalyst, leading to the corresponding fused isoquinoline compounds 4. With these considerations in mind, thus we started to explore the possibility of this transformation.



Scheme 1. Proposed synthetic route for tandem reaction of 2-alkynylbenzaldoximes 1 with carbodiimides 2.

Results and Discussion

The initial attempt was carried out with 2-alkynylbenzaldoxime **1a** with N-[(cyclohexylimino)methylene]cyclohexanamine (DCC **2a**) in the presence of 10 mol-% of Lewis

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 [[]a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China Fax: +86-21-65641740
 E-mail: ije wu@fudan edu cn

acid in various solvents at 60 °C (Table 1). At the outset, the reaction was stopped at the formation of isoquinoline *N*-oxide 3a (30% yield), and no further transformation was detected when CuI was used as the catalyst in 1,2-dichloroethane (DCE; Table 1, Entry 1). Similar results were observed when Cu(OTf)₂ (25% yield) or Zn(OTf)₂ (80% yield) was employed as a replacement (Table 1, Entries 2 and 3). A trace amount of product was generated when Bi(OTf)₃ was utilized as the catalyst under the conditions (Table 1, Entry 4). In contrast, the use of silver triflate as a catalyst in the reaction led to the formation of a product with 80%isolated yield (Table 1, Entry 5). The result could not be improved when the reaction was catalyzed by PdCl₂ or FeCl₃ (Table 1, Entries 6 and 7). However, structural identification discovered that the compound obtained was the unexpected 1,3-dicyclohexyl-1-(3-phenylisoquinolin-1-yl)urea (5a), instead of the corresponding product 4a. With this promising result in hands, we further tested the reaction in other solvents by using AgOTf as the catalyst (Table 1, Entries 8-13). Interestingly, compound 5a could be obtained in 94% yield when the reaction was performed in DMF (Table 1, Entry 10). Lower yields were generated when the reaction was carried out in other solvents. We also examined the reaction catalyzed by 5 mol-% of silver triflate in DMF at 60 °C, which resulted in lower yield. An inferior result was displayed when the reaction was carried out at 25 °C (data not shown).

Table 1. Initial studies for tandem reaction of 2-alkynylbenzaldoxime **1a** with carbodiimide **2a**.



[a] Isolated yield based on 1a.



As described above in the reaction process, isoquinoline *N*-oxide **3** was demonstrated to be the key intermediate, and indeed, this compound, which was generated from 2-alk-ynylbenzaldoxime through 6-*endo* cyclization in the pres-



Scheme 2. Possible pathway for AgOTf-catalyzed tandem reaction of 2-alkynylbenzaldoxime 1 with carbodiimide 2.

Table 2. Silver triflate catalyzed tandem reaction of 2-alkynylbenzaldoximes **1** with carbodiimides **2**.



Entry	2-Alkynylbenzaldoxime 1	Carbodiimide 2	Product	% Yield ^[a]
1	1a	2a	5aa	94
2	1a	2b	5ab	96
3	1b	2a	5ba	90
4	1b	2b	5bb	99
5	1c	2b	5cb	99
6	1d	2a	5da	71
7	1d	2b	5db	70
8	1e	2a	5ea	90
9	1e	2b	5eb	99
10	1f	2a	5fa	90
11	1f	2b	5fb	84
12	1g	2a	5ga	83
13	1g	2b	5gb	85
14	1h	2a	5ha	97
15	1h	2b	5hb	96
16	1i	2b	5ib	92
17	1j	2a	5ja	90
18	1j	2b	5jb	96
19	1k	2a	5ka	94
20	1k	2b	5kb	91
21	11	2a	5la	97
22	11	2b	5lb	93
23	1m	2a	5ma	96
24	1m	2b	5mb	99
25	1n	2a	5na	77
26	1n	2b	5nb	95
27	10	2b	5ob	88
28	1p	2b	5pb	95
29	1q	2a	5qa	97
30	1q	2b	5qb	90
[a] Isola	ated vield based on 1.			



Conclusions

Experimental Section

In summary, we have described a novel and facile route

for the generation of 1-(isoquinolin-1-yl)ureas through a sil-

ver triflate catalyzed tandem reaction of 2-alkynylbenz-

aldoximes with carbodiimides under mild conditions. The

good substrate generality, mild reaction conditions, and

high efficiency of this synthetic route would be attractive

General Procedure for Silver Triflate Catalyzed Tandem Reaction

of 2-Alkynylbenzaldoximes 1 with Carbodiimides 2: Silver triflate

(0.02 mmol, 10 mol-%) was added to a solution of 2-alkynylbenzaldoxime **1** (0.2 mmol) and carbodiimide compound **2** (0.4 mmol,

2 equiv.) in DMF (2.0 mL). The solution was stirred at 60 °C in air

overnight. After completion of the reaction as indicated by TLC,

the reaction was quenched by the addition of saturated aqueous

NH₄Cl (5.0 mL), and the mixture was extracted with EtOAc

 $(3 \times 4.0 \text{ mL})$. The combined organic layer was dried with Na₂SO₄

and concentrated in vacuo. The residue was purified by column

1,3-Dicvclohexvl-1-(3-phenvlisoquinolin-1-vl)urea (5aa): ¹H NMR

(400 MHz, CDCl₃): $\delta = 0.68-2.03$ (m, 20 H), 3.61-3.68 (m, 2 H),

4.56–4.60 (m, 1 H), 7.43 (t, J = 7.3 Hz, 1 H), 7.51–7.57 (m, 3 H),

7.69 (t, J = 7.3 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 1 H), 8.08–8.11 (m,

2 H), 8.18 (d, J = 8.3 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃):

 $\delta = 24.7, 25.4, 25.6, 26.1, 32.0, 33.3, 116.3, 125.8, 126.3, 126.7,$

127.3, 127.6, 128.8, 130.8, 138.5, 138.9, 149.9, 152.3, 156.0 ppm.

HRMS: calcd. for $C_{28}H_{33}N_{3}O$ [M + H]⁺ 428.2702; found 428.2709. **1,3-Diisopropyl-1-(3-phenylisoquinolin-1-yl)urea (5ab):** ¹H NMR (400 MHz, CDCl₃): $\delta = 0.89$ (d, J = 6.3 Hz, 6 H), 1.29 (d, J = 7.0 Hz, 6 H), 3.64 (d, J = 7.7 Hz, 1 H), 3.95–4.01 (m, 1 H), 4.97–5.01 (m, 1 H), 7.43 (t, J = 7.3 Hz, 1 H), 7.51–7.59 (m, 3 H), 7.70 (t, J = 8.3 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.06 (d, J = 8.7 Hz,

1 H), 8.11 (s, 1 H), 8.18 (d, J = 7.3 Hz, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 21.5$, 23.0, 42.3, 49.0, 116.2, 125.6, 126.0,

126.7, 127.4, 127.6, 128.8, 130.8, 138.5, 138.9, 149.9, 152.2, 156.0 ppm. HRMS: calcd. for $C_{22}H_{25}N_3O$ [M + Na]⁺ 370.1895;

chromatography on silica gel to provide product 5.

and beneficial for the construction of a focused library.

Figure 1. 2-Alkynylbenzaldoximes 1.

ence of silver triflate, was highly stable and could be isolated. As carbodiimide was a good electrophile in the reaction, the subsequent [3+2] cycloaddition would occur leading to corresponding adduct **4**, which then underwent intramolecular rearrangement to give rise to unexpected 1-(isoquinolin-1-yl)urea **5** (Scheme 2).

Under the optimized conditions [silver triflate (10 mol-%), DMF, 60 °C], we then examined the generality of this reaction, and the results are shown in Table 2. The reaction was found to afford good to excellent yields of the desired products. For instance, treatment of 2-alkynylbenzaldoxime 1a with 2b gave rise to the corresponding product 5ab in 96% yield (Table 2, Entry 2). Almost quantitative yield of compound **5bb** or **5cb** was obtained when 2-alkynylbenzaldoxime 1b or 1c was used in the reaction of carbodiimide **2b** under the standard conditions (Table 2, Entries 4 and 5). From these results, it seemed that in addition to the aromatic groups attached to the $C \equiv C$ triple bond, alkyl groups were also found to be suitable to cleanly generate the desired products. When a cyclopropyl group was attached to the triple bond, the expected products were generated in slightly lower yields (Table 2, Entries 6 and 7). This methodology could also be extended to other 2-alkynylbenzaldoximes with various substituents on the aromatic ring. For example, reactions of fluoro-, chloro-, or methoxy-substituted 2-alkynylbenzaldoxime 1 (Figure 1) with carbodiimide 2a or 2b (Figure 2) worked well to afford the desired products in good to excellent yields; the electronic nature of the aromatic backbone of the substrates did not seem to exert any influence.



Figure 2. Carbodiimides 2.

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found 370.1894.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra of compound **5**.

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