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Tandem Electrophilic Cyclization-[3+2] Cycloaddition-Rearrangement Reactions of 2-Alkynylbenzaldoxime, DMAD, and Br₂

Qiuping Ding,[†] Zhiyong Wang,[†] and Jie Wu^{*,†,‡}

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

jie_wu@fudan.edu.cn

Received September 18, 2008



Tandem electrophilic cyclization–[3+2] cycloaddition–rearrangement reactions of 2-alkynylbenzaldoximes, DMAD, and bromine are described, which afford the unexpected isoquinoline-based azomethine ylides in good to excellent yields. The products could be further elaborated via palladium-catalyzed cross-coupling reactions to generate highly functionalized isoquinoline-based stable azomethine ylides.

Methodology development and library approaches to the discovery of small-molecule enzyme inhibitors or receptor ligands are well-established.¹ Among the strategies used for the construction of small molecules, design and synthesis of natural product-like compounds via tandem reactions have attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis.² As a privileged fragment, the 1,2-dihydroisoquinoline (including isoquinoline) core is found in many natural products and pharmaceuticals that exhibit remarkable biological activities.3 Typical examples include papaverine (smooth muscle relaxant),^{3e} saframycin-B (antitumor agent),^{3f} indenoisoquinoline (topoisomerase I inhibitor),^{3g} and narciclasine (antitumor agent).^{3h} Many efforts continue to be given to the development of new 1,2-dihydroisoquinoline or isoquinoline-based structures and new methods for their constructions.⁴⁻⁶ As part of a program in our laboratory for the expeditious synthesis of biologically relevant heterocyclic

10.1021/jo802076k CCC: \$40.75 © 2009 American Chemical Society Published on Web 12/04/2008

compounds,^{6,7} we became interested in developing novel and efficient methods to construct the new 1,2-dihydroisoquinoline or isoquinoline-based structures, with a hope of finding more active hits or leads for our particular biological assays. Herein, we would like to disclose our recent efforts toward the synthesis of isoquinoline-based structures via tandem electrophilic cyclization-[3+2] cycloaddition-rearrangement reactions of 2-alkynylbenzaldoximes with DMAD. The products could be further elaborated via transition metal catalyzed cross-coupling reactions.

The electrophilic cyclization of heteroatomic nucleophiles such as oxygen, nitrogen, sulfur, and phosphorus with tethered

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SCHEME 1. Proposed Tandem Electrophilic Cyclization-[3+2] Cycloaddition of 2-Alkynylbenzaldoxime



alkynes has proven to be an effective method of preparing a large variety of heterocyclic ring systems.^{8,9} The electrophiles such as iodine, bromine, ICl, and NBS 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. Meanwhile, it was found that 2-alkynylbenzaldehyde was a versatile building block in tandem reactions for construction of heterocycles.¹⁰ Prompted by the results, we envisioned that 2-alkynylbenzaldoxime might be utilized as starting material for synthesis of N-heterocycles due to the structural similarity with 2-alkynylbenzaldehyde. Recently, we discovered that 2-alkynylbenzaldoxime 1 would be converted to isoquinoline N-oxide A via electrophilic cyclization^{7a} in the presence of electrophiles such as iodine or bromine. The resulting compound A might undergo dipolar cycloaddition in the presence of dipolarophiles leading to the fused 1,2-dihydroisoquinoline derivatives B (Scheme 1). After further transformation, functionalized fused 1,2-dihydroisoquinolines C could be generated via palladium-catalyzed crosscoupling reactions. It is well-known that the [3+2] cycloaddition reaction is a useful tool for constructing five-membered heterocyclic compounds.¹¹ To verify the practicability of this projected route, we started to investigate the possibility for onepot tandem electrophilic cyclization-[3+2] cycloaddition of 2-alkynylbenzaldoxime 1.

Initially, a set of experiments were carried out with 2-alkynylbenzaldoxime (1a) and dimethyl acetylene dicarboxylate (DMAD) as model substrates in the presence of bromine. No desired product **B1** was generated when the reaction was performed at room temperature in dichloromethane (Table 1,

(12) We thank the referee's helpful suggestion for structure identification of compound **2**.

 TABLE 1.
 Condition Screening for Tandem Electrophilic

 Cyclization-[3+2]
 Cycloaddition Reactions of

 2-Alkynylbenzaldoxime^a

\bigcirc	N-OH CO2N Ph CO2N 1a DMAI	$Me = Br_2 (1.0 ec} Base (1.2 ec} Solvent, C) Marco C$	quiv) quiv) rt CO ₂ Me	CO ₂ Me NOTO2Me Ph ^O Br 2a
			N B1 Ph	not observed
entry	base	solvent	time (h)	yield $(\%)^b$
1	none	CH_2Cl_2	24	0
2	DABCO	CH_2Cl_2	24	5
3	DBU	CH_2Cl_2	24	trace
4	pyridine	CH_2Cl_2	24	trace
5	Et ₃ N	CH_2Cl_2	24	trace
6	KOH	CH_2Cl_2	6	6
7	NaOH	CH_2Cl_2	6	15
8	LiOH	CH_2Cl_2	24	70
9	Na ₂ CO ₃	CH_2Cl_2	24	31
10	Cs_2CO_3	CH_2Cl_2	24	67
11	K_2CO_3	CH_2Cl_2	24	67
12	NaHCO ₃	CH_2Cl_2	24	40
13	KF	CH_2Cl_2	24	18
14	K_2HPO_4	CH_2Cl_2	18	87
15	K_3PO_4	CH_2Cl_2	18	82
16	NaOAc	CH_2Cl_2	24	88
17	NaOAc	$(CH_2Cl)_2$	24	74
18	NaOAc	DMF	24	10
19	NaOAc	CH ₃ CN	24	51
20	NaOAc	CH_3NO_2	24	79
21	NaOAc	THF	24	66
22	NaOAc	toluene	24	72

^{*a*} Reaction conditions: 2-alkynylbenzaldoxime **1a** (0.30 mmol), dimethyl but-2-ynedioate (1.0 equiv), bromine (1.0 equiv), base (1.2 equiv), solvent (2.0 mL). ^{*b*} Isolated yield based on 2-alkynylbenzaldoxime **1a**.

entry 1). We reasoned that during the electrophilic cyclization process, the in situ generated HBr might inhibit the reaction. Thus, the addition of base would benefit the reaction. Different bases were then screened and NaOAc was demonstrated as the best choice. Under these conditions, a product was isolated in 88% yield (Table 1, entry 16). However, after careful identification, the structure of this product was recognized as compound **2a** instead of the desired fused 1,2-dihydroisoquinoline **B1**. We also tested other solvents, such as 1,2-dichloroethane, DMF, CH₃CN, and THF (Table 1, entries 17–22). However, only inferior results were observed. According to the previous report,¹³ the fused 1,2-dihydroisoquinoline **B1** was generated as intermediate in the reaction process, which then underwent rearrangement leading to the unexpected compound **2a**.¹³

The scope of this reaction was then investigated under the optimized conditions (NaOAc, CH_2Cl_2 , rt), and the results are summarized in Table 2. For all cases, 2-alkynylbenzaldoxime **1** reacted with dimethyl acetylene dicarboxylate and bromine leading to the corresponding products **2** in good to excellent yields. For instance, reaction of 2-alkynylbenzaldoxime **1b** under the standard conditions gave rise to the corresponding product **2b** in 63% yield (Table 2, entry 2). Lower yield was obtained when compound **1c** was utilized as substrate (Table 2, entry 3, 42% yield). Reaction of 2-alkynylbenzaldoxime **1d**,

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 TABLE 2.
 Tandem Electrophilic Cyclization-[3+2]

 Cycloaddition-Rearrangement Reactions of 2-Alkynylbenzaldoximes with DMAD^a



^{*a*} Reaction conditions: 2-alkynylbenzaldoxime **1** (0.30 mmol), dimethyl but-2-ynedioate (1.0 equiv), bromine (1.0 equiv), NaOAc (1.2 equiv), CH₂Cl₂ (2.0 mL), rt, 18-24 h. ^{*b*} Isolated yield based on 2-alkynylbenzaldoxime **1**. PMP: *p*-methoxyphenyl.

DAMA, and bromine afforded the isoquinoline-based azomethine ylide **2d** in almost quantitative yield (Table 2, entry 4, 98% yield). The structure of compound **2d** was also verified by X-ray illustration (for details, see the Supporting Information). In addition, it seems that the groups attached on the aromatic ring of 2-alkynylbenzaldoxime **1** affect the reaction markedly. Compared to the electron-donating group, a better result was observed with an electron-withdrawing group attached on the aromatic ring of 2-alkynylbenzaldoxime **1**. For example, 88% yield of product **2e** was observed when fluoro-substituted 2-alkynylbenzaldoxime **1e** was employed in the reaction (Table 2, entry 5), while 52% yield of product **2f** was generated when substrate **1f** was used under the same conditions (Table 2, entry 6). When R² was replaced by alkyl groups (butyl or cyclopropyl





^{*a*} Reaction conditions: substrate **2** (0.25 mmol), arylboronic acid (1.2 equiv), $PdCl_2(PPh_3)_2$ (10 mol %), K_2CO_3 (2.0 equiv), DMF/H₂O (2.0 mL, 5/1), rt, 12 h. ^{*b*} Isolated yield based on compound **2**. PMP: *p*-methoxyphenyl.

group), reactions also proceeded well to give rise to the corresponding products in good yields (Table 2, entries 7-9).

As mentioned above, the resulting bromo-containing products **2** could be easily functionalized by using known organopalladium chemistry. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. Thus, we started to explore the possibility of the Suzuki–Miyaura coupling reaction¹⁴ by using the bromosubstituted azomethine ylide **2** as an electrophile for the synthesis of functionalized isoquinoline-based azomethine ylides. The reactions were performed at room temperature catalyzed by PdCl₂(PPh₃)₂ (10 mol %) in DMF–H₂O in the presence of potassium carbonate as base (Table 3). We found that all reactions proceeded smoothly to generate the desired product **3** in good to excellent yields.

In conclusion, we have described an efficient route for the synthesis of isoquinoline-based azomethine ylides starting from

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2-alkynylbenzaldoximes, DMAD, and bromine via tandem electrophilic cyclization–[3+2] cycloaddition–rearrangement reactions. These products could be further elaborated by Suzuki–Miyaura couplings to introduce more diversity. The efficiency of this method combined with the operational simplicity of the present process makes it potentially attractive for library construction. The focused library generation and screening for biological activity of these small molecules are under investigation in our laboratory.

Experiment Section

General Procedure for Tandem Electrophilic Cyclization-[3+2] Cycloaddition-rearrangement Reactions of DMAD with 2-Alkynylbenzaldoxime. Br₂ (0.30 mmol, 1.0 equiv) in 2.0 mL of CH₂Cl₂ was added to a mixture of 2-alkynylbenzaldoxime 1 (0.30 mmol) and NaOAc (0.36 mmol, 1.2 equiv) in CH₂Cl₂ (2.0 mL). After 5 min, dimethyl acetylene dicarboxylate (DMAD) (0.60 mmol, 2.0 equiv) was added, and the reaction was stirred at room temperature. After completion of the reaction as indicated by TLC, the solvent was diluted with CH2Cl2 (10 mL), washed with saturated aqueous NaS₂O₃ (20 mL), and dried by anhydrous Na₂SO₄. Evaporation of the solvent followed by purification on silica gel provided the corresponding product 2. Selected example, compound **2a**: yield 88%; ¹H NMR (400 MHz, CDCl₃) δ 3.46 (s, 3H), 3.73 (s, 3H), 7.34 (d, J = 7.3 Hz, 1H), 7.44–7.48 (m, 1H), 7.49–7.53 (m, 3H), 7.97 (t, J = 8.3 Hz, 1H), 8.22 (t, J = 8.0 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 8.46 (d, J = 8.8 Hz, 1H), 9.33 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 50.4, 51.8, 124.3, 127.3, 127.5, 127.6, 128.3, 128.4, 128.9, 130.4, 130.6, 131.0, 132.6, 137.9, 138.0, 150.0, 154.4, 167.9, 171.6; HRMS calcd for $C_{21}H_{16}BrNO_5$ [M + H]⁺ 442.0290, found 442.0301.

General Procedure for the Synthesis of Functionalized Isoquinoline-Based Azomethine Ylides via Palladium-Catalyzed Suzuki Reactions. A solution of compound 2 (0.25 mmol), ArB(OH)₂ (0.30 mmol, 1.2 equiv), K₂CO₃ (0.5 mmol, 2.0 equiv), and PdCl₂(PPh₃)₂ (0.025 mmol, 10 mol %) in H₂O/DMF (1:5, 2.0 mL) was stirred at room temperature overnight. After completion of the reaction as indicated by TLC, the solvent was diluted with EtOAc (30 mL), washed with aqueous HCl (1.0 M, 10 mL), and dried by anhydrous Na₂SO₄. Evaporation of the solvent followed by purification on silica gel provided the corresponding compound 3. Selected example, compound 3a: yield 78%; ¹H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 3.74 (s, 3H), 6.96 (br, 1H), 7.00 (d, J = 7.8Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 7.20–7.32 (m, 5H), 7.37 (t, J= 7.8 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.89 (t, J = 7.3 Hz, 1H), 7.97 (t, J = 8.3 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 9.36 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 50.3, 51.7, 126.4, 126.8, 127.4, 127.5, 128.0, 128.3, 128.5, 129.2, 129.4, 129.7, 130.0, 130.2, 131.3, 133.6, 136.3, 138.3, 138.4, 148.7, 153.9, 168.1, 171.8; HRMS calcd for $C_{27}H_{21}NO_5$ [M + H]⁺ 440.1498, found 440.1508. (For details, please see the Supporting Information.)

Acknowledgment. Financial support from the National Natural Science Foundation of China (20772018), Shanghai Pujiang Program, and Program for New Century Excellent Talents in University (NCET-07-0208) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and copies of ¹H and ¹³C NMR of compounds **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802076K